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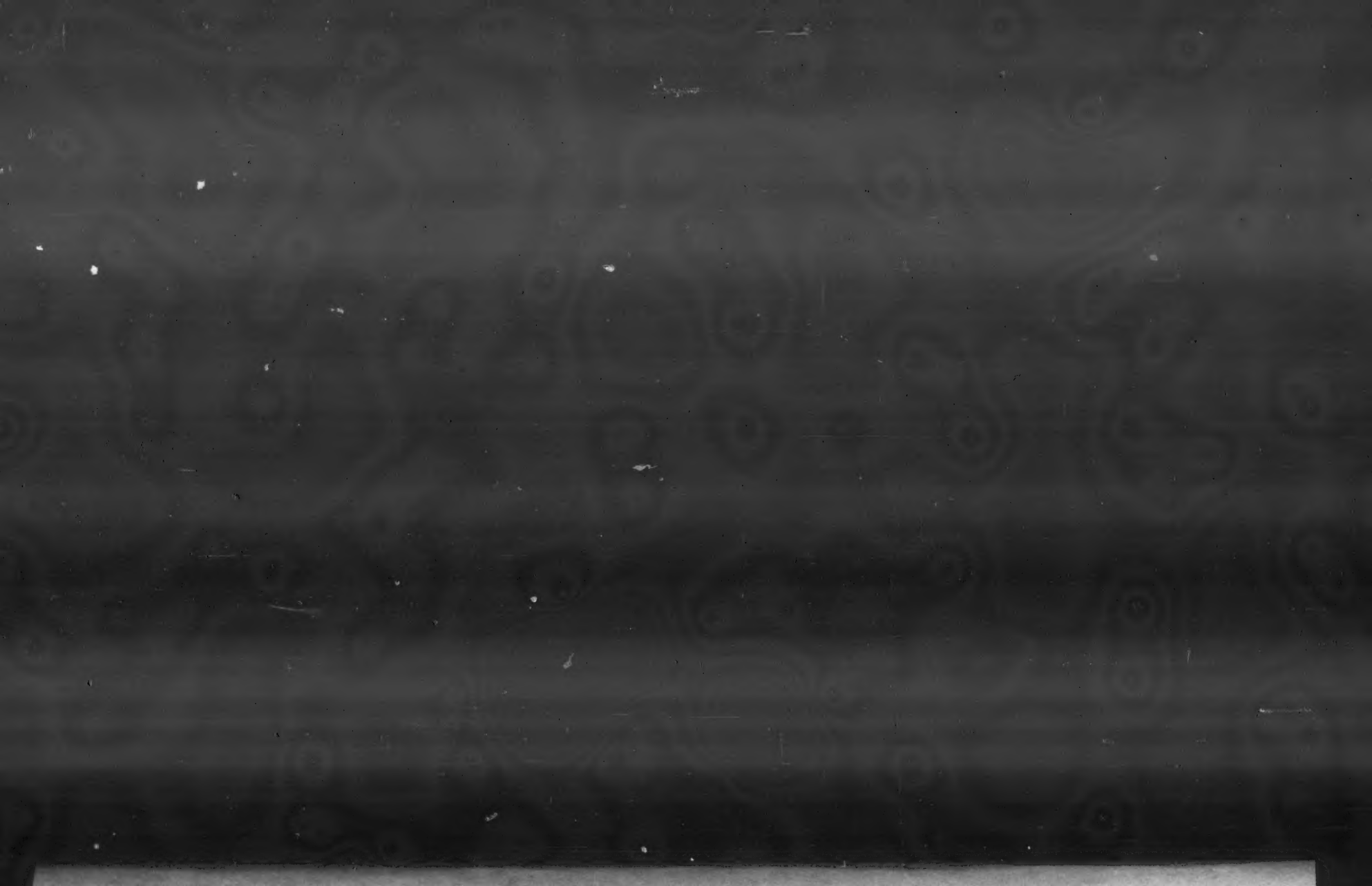

The American Heart Journal

VOL. IX OCTOBER, 1933 No. 1

Original Communications

INTERAURICULAR SEPTAL DEFECT ASSOCIATED WITH MITRAL STENOSIS*

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A POST-MORTEM examination recently revealed to us an unsuspected combination of cardiac lesions that may well be recognized before death if the possibility of this diagnosis be kept in mind. A stenosed mitral valve coexisting with an interauricular septal defect was demonstrated in the heart, the roentgenogram of which appears to be distinctive. This combination of lesions like many other cardiac abnormalities has been described in the past, but it is worth while to discuss it from the viewpoint of our more modern methods of establishing clinical diagnoses and to summarize cases already reported, mostly by the French.

The increasing knowledge of individual malformations of the heart is rapidly approaching the point where the inclusive diagnosis of congenital heart disease alone is inadequate and lacks the descriptive terminology so useful in our medical nomenclature.

LITERATURE

The literature contains the reports of 23 cases in which mitral stenosis is associated with some degree of deficiency of the interauricular septum (Table I). Martineau[20] presented the first case in 1865 and so preceded a long series of contributions from the French investigators. The following year (1866) Peacock[22] included a similar case in his book *Malformations of the Heart*. There then appeared in sequence reports of cases by Wagstaffe[26] (1868), Chénieux[7] (1870), Chouppe[8] (1872), Firket[13] (1880), Butin[5] (1893), Huchard and Bergouignan[16] (1901), Griffith[14] (1902), Tylecote[25] (1903), Söldner[23] (1904), Moureyre[21] (1911), Dufour and Huber[12] (1911) and Heitz[15] (1912). In 1916,

*From the Cardiac Clinic and Laboratory of the Massachusetts General Hospital.

a year after Abbott's[1] case report (1915), Lutembacher[19] reviewed the subject at length and discussed the various viewpoints held as to the probable etiology of the condition and the consequent alterations in the hemodynamics. As a result of his paper, the association of mitral stenosis with an interauricular septal defect has become commonly known as Lutembacher's disease. Following this, other cases have been added to the literature by Cramer and Frommel[9] (1923), Donnally[10] (1924), Cabot[6] (1928), Langerhon and Loheac[18] (1928) and Wahl and Gard[27] (1931). Recently Dressler and Rösler[11] presented a valuable communication on the subject (1930) in which they presented a new case and described what they maintain to be typical roentgen ray findings. Theses upon the condition have been written by Bonnabel[4] in 1906 and by Souza Gularte[24] in 1924.

CASE REPORT

An American letter carrier, single, fifty-six years of age, entered the Massachusetts General Hospital in June, 1932, complaining of shortness of breath, weakness, and swelling of the legs and abdomen for four years.

He had always been well except for occasional sore throats; there was no history of rheumatism, chorea, typhoid fever, or pneumonia. His father died of a lung infection, and his mother was in fair health at eighty-three years of age. Two sisters were in good health but five other siblings died in infancy.

Three years previously he had been forced to give up his position because of the same symptoms of which he complained on admission to this hospital, and at that time he had been told that he had an enlarged heart and that an x-ray picture had been suggestive of Hodgkin's disease, for which he subsequently received x-ray treatments. The physical examination in 1929 showed visible jugular pulsations, an enlarged heart with the left border in the midaxillary line, a loud systolic murmur at the mitral area transmitted to the axilla, and an arrhythmia. The abdomen was rounded and a fluid wave was obtained. Slight pitting edema was observed in both ankles. Within two months an abdominal paracentesis was done twice with the removal of amber colored fluid, following which a mass could be palpated four fingers below the costal margin. Digitalis was given and the edema partially disappeared until a return of symptoms followed an upper respiratory infection nine months ago. Since then there had been a progressive increase in his failure, and he was admitted in extremis to the Massachusetts General Hospital, where he died nine hours later.

The physical examination on entry nine hours before death showed a poorly developed man of normal height, having a grayish color, marked orthopnea, and slightly distended neck veins. The heart was enlarged to the left, and systolic and rumbling diastolic murmurs were heard at the apex without palpable thrills. The heart sounds and the pulse were of poor quality. Auricular fibrillation was present. Arteriosclerosis of the large vessels was noted and the blood pressure was recorded at 130 mm. mercury systolic and 70 diastolic. Moist râles were heard at both lung bases. There were massive edema below the waist and marked ascites. An abdominal paracentesis was done with the removal of 3100 c.c. of a slightly yellow and turbid fluid. The red count was 4,950,000, white count 7,750, and hemoglobin 90 per cent.

The x-ray film taken August 22, 1929, showed the heart shadow to be tremendously enlarged, the shadow of the right auricle being particularly prominent. There was

also a marked prominence of the pulmonary conus. The only portion of the aorta visible was the knob which was rather small. There was extensive increase in the size and density of the hilus shadows on both sides, probably due to dilated pulmonary vessels.*

The post-mortem examination was performed five hours after death. The subject was a fairly well developed but poorly nourished, middle-aged man weighing about 160 pounds. There was marked pitting edema of the lower extremities and hips with a purplish discoloration of the legs. There was a marked bluish discoloration of the face and mucous membranes.

The peritoneal cavity contained 400 c.c. of clear yellow fluid, the pericardial and left pleural cavities 100 c.c. each. The right pleural cavity was entirely obliterated by adhesions. The right lung was rather spongy but was crepitant throughout, whereas the left was crepitant except for a pyramidal area in the

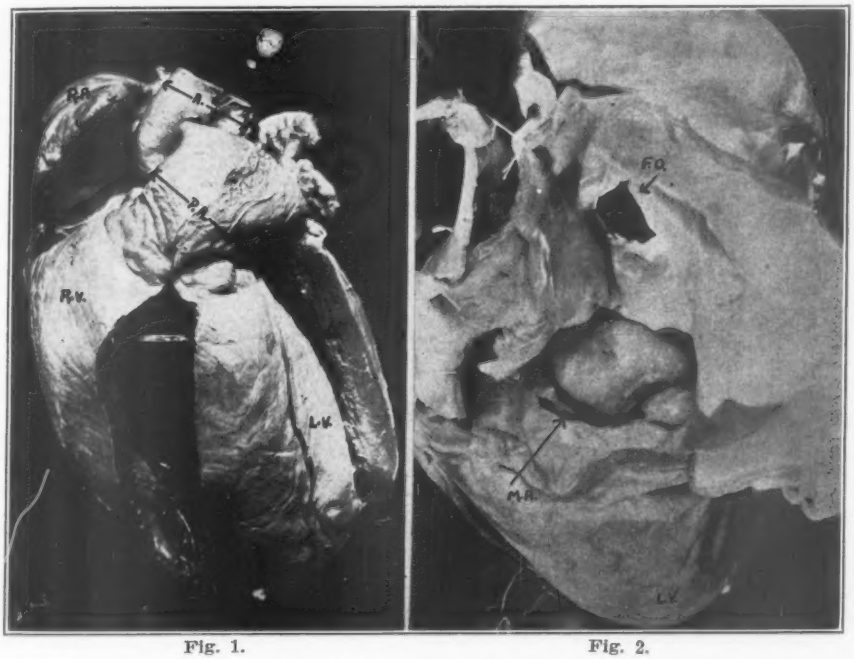

Fig. 1. Fig. 2.

Fig. 1.—Heart of present case of interauricular septal defect with mitral stenosis. *R.A.*, right auricle; *R.V.*, right ventricle; *L.V.*, left ventricle; *A*, aorta; *P.A.*, pulmonary artery. Note in particular the large right ventricle and pulmonary artery.

Fig. 2.—Same heart as shown in Fig. 1, with view into the left auricle from above. *M.A.*, aperture of the stenosed mitral valve; *F.O.*, patent foramen ovale; *L.V.*, left ventricle.

lateral part of the upper lobe typical of an infarct. The liver weighed 1100 gm. and showed very little congestion. The cervical and inguinal nodes were negative but one axillary gland was palpable.

The heart was greatly enlarged, weighing 675 gm. On external examination a marked disproportion in the size of the right and left sides of the heart was apparent. The normal relation was reversed, the right ventricle being almost three times the size of the left. On being opened the right ventricle was found to be markedly dilated to eight or ten times the normal size and its wall was greatly thickened,

*X-ray film studied through the courtesy of the St. Elizabeth's Hospital, Boston, and interpretation kindly made for us by our colleague, Dr. George W. Holmes.

measuring 8 mm. In contrast the left ventricle was only slightly dilated and its wall was only 11 mm. in width. Both auricles were enlarged but the enlargement was greater on the right side. The right auricle measured in empty state and after fixation 11×7×6 cm. The left auricle measured roughly 9×6×4 cm. A number of scattered irregular opaque whitish milk like patches were present on the endocardial surface, chiefly of the right ventricle.

The mitral valve showed marked thickening and interadherence of the cusps producing an extreme degree of stenosis, the narrowed orifice measuring approximately 1.5 cm. in length and 3 to 5 mm. in width. There was extensive calcification of the entire ring of the mitral valve. A small (6×10 mm.) irregular nodular calcified mass projected on the undersurface of the anterior cusp and a larger calcified mass projected below and behind this downward into the ventricular muscle and extended anteriorly into the interventricular septum. The chordae tendineae were shortened and thickened.

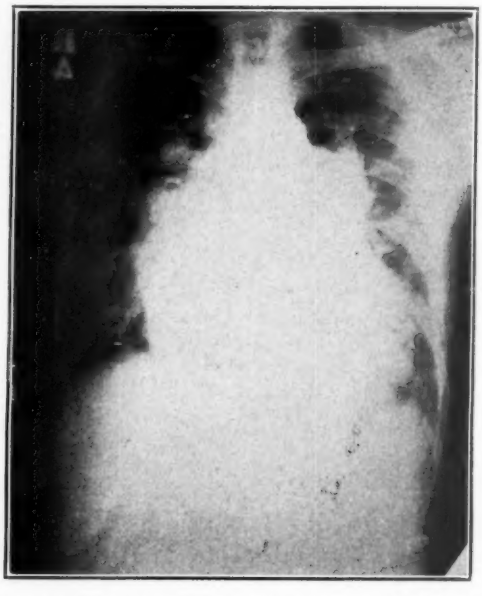

Fig. 3.—Roentgenogram of thorax of present case of interauricular septal defect with mital stenosis taken three years before death. Anteroposterior view. Note very large heart with marked prominence of pulmonary artery and lung hilus shadows.

All three cusps of the aortic valve showed slight diffuse thickening, most marked along the lines of closure. There was extensive fusion of the adjacent edges of the anterior and right posterior cusps with a firm, slightly nodular calcified deposit in the adherent area.

The pulmonary valve ring was markedly dilated, measuring 9.5 cm. in circumference. Except for slight thickening in the central portions of the free margin the cusps were normal.

The tricuspid valve showed slight to moderate diffuse patchy thickening most marked along the free margins. Some of the chordae tendineae were thickened and slightly shortened.

Connecting the cavities of the two auricles there was a large oval defect in the interauricular septum in the position of the foramen ovale. This measured in the

fixed specimen 2.4 cm. in the base-apex axis and 1.5 cm. transversely. The margin was sharp. The edge consisted for a width of 2 to 3 mm. of thin smooth whitish tissue of about the texture and consistency of a normal heart valve.

The coronary arteries were large with only slight atheroma. The aorta showed moderate atheroma without calcification and was 8.5 cm. in circumference in the ascending portion, 5.6 cm. in the arch, and 4.7 cm. in the descending part. The pulmonary artery was greatly dilated, measuring 10.5 cm. in circumference at a point 1 cm. above the pulmonary orifice. It was thickened with a smooth, yellowish surface and with only the slightest trace of atheroma in its smaller branches.

DISCUSSION

Pathogenesis.—An interauricular septal defect may be one of several types. The septum may be entirely lacking or represented only by a narrow remnant encircling the auricular walls. Such a condition exists when in fetal life the lower part of the auricular septum fails to develop normally. This defect is spoken of as a persistent ostium primum and when it is extreme produces a true triloculate heart. A deficiency of the upper part of the auricular septum above the foramen ovale, which may or may not be patent, is known as a persistent ostium secundum. The foramen ovale remains patent when the primary and secondary auricular septa fail to meet or is said to be probe-patent when they meet but do not become adherent to each other, leaving an oblique passage between them. It is possible for these commonly seen probe-patent foramina ovales to become frankly patent and allow the free flow of blood through them if the septum should be greatly stretched due to distended and dilated auricles. Such were the cases reported by Martineau, Chénieux, and Butin.

In fetal life, the course of the flow of a considerable portion of blood in the heart is from the right auricle through the patency in the interauricular septum to the left auricle, and thence to the left ventricle which expels its contents into the aorta. After birth the adult type of circulation is established, and since nearly equal pressures are maintained within both auricles under normal conditions little or no admixture of blood takes place in very early life even though there may be a small opening in the septum between the auricles.

If, however, the interauricular septal defect should be complicated by some obstruction to the normal direction of blood flow as by mitral stenosis, there would be a change in the hemodynamics. The left auricular pressure would be increased over that in the right auricle with a resulting flow of blood from left auricle to right auricle. The blood is sent through the pulmonary circuit for the second time; and later, when the right auricular pressure increases sufficiently, the blood may be backed up into the venae cavae to increase the hepatic, portal and peripheral venous pressure. Under such circumstances the chambers of the right side of the heart are doing more work than are those of the left; consequently dilatation and hypertrophy of the right

auricle and ventricle and dilatation of the pulmonary artery follow, whereas the left ventricle and the aorta remain small. A similar condition exists in hearts having uncomplicated interauricular septal defects (but not to such an extreme degree as when mitral stenosis is present), which would indicate that the systolic pressure in the left auricle exceeds that in the right to some extent (the left auricle is the more uniformly muscular sac). Eventually the right ventricle may fail and the pressure within its corresponding auricle is then elevated to the point where a reversal of flow from right to left takes place. This extensive admixture of arterial and venous blood explains the occurrence of "cyanose tardive" first described by Bard and Curtillet; it is found so frequently in the terminal illnesses of patients having defects of the interauricular septum that it is almost pathognomonic of that condition. Thus is explained the absence of cyanosis in patients having this anomaly until failure of the myocardium occurs. It is reasonable to expect that extensive paradoxical embolism would take place only in the presence of some degree of cyanosis, since the flow of blood must be from the right auricle to the left; very small septal defects would permit the passage of only small emboli and would cause little or no cyanosis.

Opinions as to the relationship of the mitral stenosis and the interauricular patency have been varied. Firket[13] in 1880 believed that the combination was due to a congenital malformation of the mitral valve and that the abnormality of the interauricular septum was a fortunate coincidence since it served as a safeguard against pulmonary congestion. Lutembacher[19] considered the associations of lesions to be more than coincident or independent congenital abnormalities; he maintained that the foramen ovale was prevented from closing by the elevated left auricular pressure due in turn to the stenosed mitral valve, with resulting left to right flow of blood which was opposite to the usual intrauterine circulation. Dressler and Rösler,[11] on the other hand, contend that an increased pressure in the left auricle would ordinarily favor the closure of the foramen ovale because of the oblique course of its canal. According to this interpretation, the congenital interauricular septal defect, small at first, but actual and not potential, would be complicated by an acquired mitral endocarditis causing stenosis of the valve, and this in time would by stretching convert a small interauricular septal patency into a larger one. We agree with these conclusions of Dressler and Rösler. Mitral stenosis would be more often complicated by open patency of the foramen ovale if these two lesions were not primarily coincidental.

Two cases of fetal endocarditis resulting in mitral stenosis at birth have been reported independently by Kockel[17] and by Ayrolles.[2] The foramina ovales in these hearts were described as being patent to the passage of a probe, Ayrolles' case allowing water to flow from the

right to the left auricle but not in the other direction. Another case of fetal endocarditis causing mitral stenosis was reported by Donnally,[10] in which he states that the foramen ovale was small and guarded by a thick fold. He believes that the course of blood flow was from the left auricle to the right side of the heart and then into the systemic circulation through a patent ductus arteriosus. The pulmonary artery in this case continued as the dorsal aorta after giving off the ductus arteriosus and two pulmonary branches while the aorta remained as an example of infantile coarctation.

Clinical and Pathological Data.—The combination of mitral stenosis and interauricular septal defect is rare, only twenty-three cases having been reported in the literature; two cases, the new one reported here and the case already reported by Cabot,[6] have been found by us in a review of 6800 autopsies at the Massachusetts General Hospital. The condition is found almost entirely in women; of the 23 cases in the literature the patient of Söldner[23] with a persistent ostium primum is the only male. Our case is the second male known to have had this condition. The lesion can be well tolerated as is indicated by the patient of Firket[13] who died at seventy-four years of age having had eleven pregnancies, and the patient of Lutembacher[19] who died at sixty-one years after seven pregnancies. Nevertheless, 11 of the 24 patients died at thirty years of age or under; the average age at death was thirty-five years, which is somewhat under that for mitral stenosis alone. The type of individual is usually below the normal average physically, being described as delicate, poorly developed, or infantile. Disorders of menstruation or tuberculosis have been noted commonly. The French believe that the general underdevelopment is due to the hypoplastic aorta and the consequent smaller blood supply. The history of rheumatic fever was definite in 3 of the 24 cases.

The physical findings are so variable that the clinical diagnosis cannot be made with confidence. Cyanosis was present in 17 of the 24 cases collected here; it appeared with the onset of failure in all except one, the case of Griffith[14] whose patient became "blue in the face" upon running. Our case showed extreme post-mortem lividity but the report of the physical examination noted only a peculiar grayish color before death. Some authors have emphasized the point that cyanosis may be absent terminally. Clubbing was seen in only one case.

An apical systolic murmur was heard in 15 cases and was the most common auscultatory finding. It was accompanied by a diastolic murmur maximal at the apex in eight cases, and by an apical thrill in four, of which two were continuous, one systolic, and the timing of the other was not noted. Mitral diastolic murmurs were heard alone in four individuals, and in three of these there were palpable presystolic thrills. Systolic murmurs were heard at the base of the heart in four

TABLE

INTERAURICULAR SEPTAL DEFECTS

NAME OF AUTHOR	DATE OF REPORT	SEX	AGE AT DEATH	CYANOSIS	MURMURS				THRILL	SIZE OF PULSE	HEART WEIGHT	SIZE OF MITRAL VALVE	OTHER VALVE INVOLVEMENT		
					SYSTOLIC		DIASTOLIC						AORTIC	TRICUSPID	PULMONARY
					APEX	BASE	APEX	BASE							
PATENT FORAMEN OVALE															
Martineau	1865	F	28	+	+	+	+	+	+					+	
Peacock	1866	F	16	+							230	8.1 cm.			
Chénieux	1870	F	27		+						720				
Chouppe	1872	F	48		+	+				Small	470	Tips of two fingers	+	+	
Firket	1880	F	74	+	+					Small			+ St.	+ In.	
Butin	1893	F	32	+	+					Small	480	Finger tip	+		
Tylecote	1903	F	43	+	+		+				660	Two finger tips			
Dufour and Hubert	1911	F	26				+		+	Small		Fibrous stenosis			
Heitz	1912	F	43	+						Small	440	Finger tip		+ In.	+
Abbott	1915	F	38	+			+		+			Button hole			
Lutembacher	1916	F	61	+	+		+			Small		Rigid cone			
Cramer and Frommel	1923	F	41		+		+		+					+ In.	
Donnally	1924	F	57 hr.	+		+						Funnel shaped			
Langerhon and Loheae	1928	F	54	+	+		+				540	Half-moon		+ In.	
Dressler and Rösler	1930	F	30	+	+					Small		Fusion of leaflets			
Wahl and Gard	1931	F	21	+			+		+		623	4.5 cm.			
McGinn and White	1933	M	56		+		+			Small	675	Marked stenosis	+	+	+

I

WITH MITRAL STENOSIS

DILATED				HYPERTROPHIED							
RIGHT AURICLE	LEFT AURICLE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT AURICLE	LEFT AURICLE	RIGHT VENTRICLE THICKNESS OF WALL	LEFT VENTRICLE THICKNESS OF WALL	SIZE OF PULMONARY ARTERY	SIZE OF AORTA	SIZE OF INTER-AURICULAR OPENING	REMARKS ABOUT THE INTERAURICULAR OPENING
				+	+			Normal	Small	Not stated	Patency due to distended auricles. Clot found in foramen ovale.
+	+	+				+				Admits a shilling	Entirely unclosed.
+	+	+	+							Admits a finger tip	Patency due to dilatation of the auricles.
+		+					2 cm.		Small	Admits a thumb	Widely open foramen ovale.
+	+	+	+							1×2.5 cm.	Foramen ovale open.
+		+	Small				Small	Large	Small	1 cm. × 7 mm.	Closed by thin membrane except for opening in anterior part; opening due to dilated auricles.
+	+			+	+					2 inches diam.	Round foramen ovale.
										4 cm. diam.	Patent foramen ovale.
+	+						Small			Slit opening	Foramen ovale open due to dilated auricles. Holes in posterior membrane allow direct communication.
+	+	+		+	+	+		9 cm. circum.	7 cm. circum.	2×1.5 cm.	Gaping foramen ovale incapable of closure.
+	+	+	Small	+		+	Small	Large	Small	3×4.5 cm.	Foramen ovale open.
+		+		+		11 mm.	11 mm.	9 cm. circum.	3.6 cm. circum.	3×5×2 cm.	Foramen ovale open.
+		+			Small		Small			Small	Foramen guarded by a fold but freely open into the right auricle. Ductus arteriosus patent. Infantile coarctation of aorta.
+	+	+	Small	+	+	+	Small			Admits a franc piece	Foramen ovale open.
+		+		+		+	Small	10 cm. circum.	4 cm. circum.	3×4 cm.	Foramen ovale open.
						20 to 35 mm.	10 to 15 mm.	4.3 cm. diameter	1.6 cm. diameter	22 mm. diameter	Foramen ovale wide open.
+	+	+		+	+	8 mm.	11 mm.	10.5 cm. circum.	8.5 cm. circum.	2.4×1.5 cm.	Patent foramen ovale with sharp edges.

TABLE

NAME OF AUTHOR	DATE OF REPORT	SEX	AGE AT DEATH	CYANOSIS	MURMURS				THRILL	SIZE OF PULSE	HEART WEIGHT	SIZE OF MITRAL VALVE	OTHER VALVE INVOLVEMENT		
					SYSTOLIC		DIASTOLIC						AORTIC	TRICUSPID	PULMONARY
					APEX	BASE	APEX	BASE							
INTERAURICULAR SEPTAL DEFECT—PERSISTENT OSTUM PRIMUM.															
Huchard and Bergouignan	1901	F	34	+		+	+	+				Finger tip	+	+	+
Griffith	1902	F	13	+	+		+		+		700	Stenosis			
Tylecote	1903	F	39	+			+			Weak	1100	Fibrous stenosis			
Söldner	1904	M	30		+							Aortic leaf thick			
INTERAURICULAR SEPTAL DEFECT—PERSISTENT OSTIUM SECUNDUM															
Wagstaffe	1868	F	52									Finger tip	+ St.	+ In.	
PATENT FORAMEN OVALE AND AN ADDITIONAL INTERAURICULAR SEPTAL DEFECT															
Moureyre	1911	F	29	+	+					Small	550	Rigid ring		+ In.	
Cabot	1926	F	24	+	+		+		+	Poor	665	7 cm. circum. deformed	+	+	+

cases, accompanied by early blowing diastolic murmurs in two. The pulse was never described as being of good quality; it was frequently found to be irregular. Two cases had electrocardiograms which showed right axis deviation.

The post-mortem examinations have shown large hearts with weights far above normal. Tylecote's[25] patient had a heart weighing 1100 gm. but this included the adherent pericardium. The cardiac enlargement has been found to be due primarily to dilatation and hypertrophy of the right auricle and ventricle. The left auricle frequently shows similar changes, but the left ventricle is usually of small size. Dilatation of the pulmonary artery in the presence of a small aorta is common, this relationship having been observed in 13 cases. The extent of the mitral stenosis and the degree of the interauricular patency have varied considerably as is indicated in Table I.

I—CONT'D

DILATED				HYPERTROPHIED				SIZE OF PULMONARY ARTERY	SIZE OF AORTA	SIZE OF INTER-AURICULAR OPENING	REMARKS ABOUT THE INTERAURICULAR OPENING
RIGHT AURICLE	LEFT AURICLE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT AURICLE	LEFT AURICLE	RIGHT VENTRICLE THICKNESS OF WALL	LEFT VENTRICLE THICKNESS OF WALL				
+	+	+		+	+	+	+		Small	4×5 cm.	Septum consists only of a fine ridge around auricular wall.
+	+	+	+					2¼ in. circum.	1½ in. circum.	1½×2½ in. circum.	Septum absent except for a remnant of fenestrated membrane.
+		+		+		+		Large	Small	2 inches	Septum absent except for a remnant on the anterior wall.
+		+		+	7 mm.	17 mm.	17 mm.	6.7 cm. circum.	5.2 cm. circum.	1.5 cm. diam.	Membrane across foramen ovale. Hole surrounded by a membrane just above aortic cusp of the mitral valve.
	+		+		+		+			Large	Large aperture 1 inch below the superior vena cava. Foramen ovale closed.
+	+	+				+			Small	Large and small	Small perforation in anterior membrane.
+		+				6 mm.	9 mm.	Large	Small	1 cm. diam. and finger tip	Hole admitting finger tip in septum above patent foramen ovale.

Roentgenography.—The consistent pathological findings might be expected to give correspondingly consistent roentgenograms. Cramer and Frommel[9] described the heart as being a "coeur en sabot" with a prominent pulmonary arc. Lutembacher commented upon the enlargement of the right chambers, which he believed caused the apex to be blunt and raised above the diaphragm whereas in pure mitral stenosis the left border of the heart is more vertical. The report in Cabot's[6] case is quoted as follows: "The x-ray showed a mass which did not pulsate at the right of the heart. The pulsations of the heart itself were very indistinct. The outline of the heart shadow with the poor pulsation suggested pericardial disease. There was extensive mottling extending out from both lung roots."

Dressler and Rösler[11] have noted the presence of a narrow aorta with a consequent diminution of the shadow of the aortic knob in ad-

dition to the other findings. They consider the appearance of the heart to be that either of pure mitral stenosis or of an interauricular septal defect alone but with an exaggeration of all the findings due to the combined effect of the two lesions. They insist that all the features mentioned above are essential to the diagnosis; these features include the large pulmonary conus, the narrow aorta, the extensive right-sided hypertrophy, and the wide lung hilus shadows. The roentgenogram of our case conforms to their criteria and agrees in detail with the orthodiagram included in the thesis of Souza Gularte. The report of Wahl and Gard[27] is accompanied by reproductions of the roentgenograms in their case. The consistency of this x-ray evidence is convincing. It is of interest to observe that so dense are the mediastinal shadows that two cases were actually given x-ray radiation for tumors of the mediastinum and one of them subsequently underwent an operation in an attempted surgical removal of the suspected growth, which proved to be the dilated pulmonary artery.

SUMMARY

1. The clinical and pathological findings in 24 cases showing the combination of mitral stenosis and interauricular septal defect have been summarized herewith; these include the 23 cases previously reported in the literature and a new case of our own (a man fifty-six years old).

2. The abnormal alterations in the blood flow through the heart have been described.

3. The diagnosis of this combination of lesions may be made from the fairly typical roentgenogram and suggestive clinical signs. The roentgenogram corresponds with the post-mortem findings showing a large rounded heart especially prominent to the right, an exaggerated pulmonary conus, wide lung hilus markings, and a narrow aorta.

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PAROXYSMAL PULMONARY HEMORRHAGES*†

The Syndrome in Young Adults With Mitral Stenosis

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SEVERE paroxysmal pulmonary hemorrhages, not due to intrinsic disease of the lungs, are very infrequent in patients with chronic rheumatic valvular heart disease and mitral stenosis. Only 3 of the last 1000 patients with mitral stenosis admitted to the Montefiore Hospital gave a history of such recurrent pulmonary hemorrhages. Of these, 2 were females and 1 was a male.

The syndrome is characterized by the sudden onset of cough with profuse bright red expectoration in an afebrile and usually ambulatory patient with mitral stenosis in whom, as a rule, there is little evidence of congestive heart failure. The respirations and pulse are increased, the breathing may be of the asthmatic type, there is profuse sweating, and the bleeding may be very abundant although inconstant. It may come in spurts and last as long as four days at one time. It may recur periodically each month and in young girls it has been mistaken for vicarious menstruation.

While the symptom complex has been variable in each particular case, the clinical picture of all, as observed over a prolonged period of time, has been so strikingly uniform that it has been thought worth while to describe some of these cases in detail. The prognosis as to life of these younger patients with paroxysmal hemorrhages associated with mitral stenosis, once the symptom complex has appeared, is very grave.

REPORT OF CASES

Case 1.—History No. 1249-R. Diagnosis: C.R.C.V.D., mitral stenosis and insufficiency, and paroxysmal pulmonary hemorrhages.

F. S., a young woman, aged twenty-two years, was admitted to the Montefiore Hospital on November 21, 1924, and died on April 29, 1930.

Previous History.—At the age of thirteen she had a bout of chorea with the movements limited to the right side of the body. She was advised at that time to have her tonsils removed but tonsillectomy did not abolish her choreiform movements, although they were much milder for the next three years. In September, 1923, when she was sixteen, she entered a hospital because of severe palpitation of the heart and after remaining there for eight weeks, she was sent to a convalescent home. One year later she entered the Montefiore Hospital because of extreme restlessness, irritability, and palpitation of the heart.

Physical Examination.—On admission the patient appeared to be tall and poorly-nourished for her age. She showed marked twitchings of her fingers and of her right arm. The neck veins were not distended. There was a bulging of the left

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half of the chest in the region of the third, fourth, and fifth costosternal junctions. The apical impulse of the heart was in the fifth intercostal space to the left of the midclavicular line. The first heart sound was accentuated and was preceded by a rough rumbling diastolic murmur. P_2 was loud. The heart rate averaged 118 beats per minute, and there was marked sinus arrhythmia. The blood pressure was 120/90. The lungs were clear. The liver and spleen were not palpable, and there was no edema of the lower extremities.

The laboratory findings, including the blood Wassermann reaction, were negative.

Radiographic examination of the chest failed to show any abnormalities of the lungs. The left ventricle was slightly rounded, and there was a bulging of the pulmonary artery. The left auricle encroached upon the retrocardiac space. The electrocardiogram showed right axis deviation, with T_2 and T_3 negative. (The patient was not receiving any digitalis.)

Course and Progress.—During her first few weeks in the hospital she remained in bed most of the time because of the marked increase in her pulse which always averaged over 100 beats per minute. However, since she was afebrile and her heart rate was noted to be under 60 when she was sound asleep, the girl was discharged on August 9, 1925, and advised to report to the clinic. She remained well and was up and about until April 14, 1927, when she was readmitted with a severe pain in the right groin and a sharp, lancinating pain in the right scapular region.

On this day she had taken a short walk when she became suddenly aware of being unable to catch her breath. She hailed a taxicab and while riding home, her breathing became very labored and she began to expectorate large amounts of blood-tinged sputum. She was rational and not alarmed. Throughout her trip home she was forced to cough because of severe irritation in the throat. The labored breathing and expectoration stopped with rest in bed, but on the morning of April 18, 1927, while she was in the hospital, she experienced a very severe hemorrhage from the lungs.

When seen at this time, her face was ghastly white. There were large beads of perspiration on her forehead. Respirations were rapid, averaging 34 per minute, and there was a profuse bright red, bloody discharge coming out from her mouth and through her nostrils. Frequently, at irregular intervals, there would be a sudden rasping cough, accompanied by large gushes of bloody fluid. The pulse was rapid and thready and averaged 170 beats per minute, but the rhythm was regular. The heart sounds were inaudible. The lung fields revealed large, moist, bubbling râles. The liver did not enlarge.

This seizure of blood spitting lasted about half an hour, after which she sat up in a chair and felt easier. On the same evening, however, she had another hemorrhage which lasted forty-five minutes after the administration of large doses of morphine sulphate. On the following morning her breathing was asthmatic in type. Expiration was prolonged and inspiration was difficult. There was still some cough with bright red expectoration but not so severe as on the previous day. Such mild bloody expectoration continued for the next five days. During all this time she was kept warm with blankets and given fluid parenterally, since she vomited almost everything she took by mouth.

On the morning of May 1, 1927, she began to complain again of pains in the groins with right scapular tenderness, and within one hour she suffered another very severe hemorrhage. This was as abundant as one of the large and profuse hemorrhages that are seen in patients with tuberculosis. A series of drugs were tried to prevent any further bleeding, but they were all of no avail. She ceased to spit any blood-tinged sputum five days later.

During this episode a radiographic examination of her chest was reported as revealing "partial consolidation" of both lower lobes with more extensive involve-

ment on the right side. All lung signs cleared, however, within a few days, and in two weeks she was ambulatory and feeling well again.

Between this time and April 29, 1930, when she died with signs of "bronchopneumonia," she experienced several such hemorrhages from the lungs, each of which came on suddenly, without any warning, and was associated with severe breathlessness and marked palpitation of the heart, cough, and bright red, bloody expectoration. Occasionally, she complained of pains in the groins and between the scapulae. None of these seizures was accompanied by fever or leucocytosis. There was never any enlargement of the liver or edema of the lower extremities, and at no time were there any friction rubs audible over the chest. Moist râles throughout the lung fields were present at some time or other during her entire stay in the hospital after the appearance of these episodes. Jaundice, such as is often seen to follow infarction of the lung, was never present.

A necropsy was not obtained.

CASE 2.—History No. 16131-R. Diagnosis: C.R.C.V.D., mitral stenosis and insufficiency, paroxysmal pulmonary hemorrhages.

H. G., a girl aged eighteen years, was first admitted to the Montefiore Hospital on November 19, 1928, and died on July 13, 1930.

Previous History.—At the age of ten she was advised that she had heart disease, but it was not until four years later that she entered a hospital. Her chief complaints at that time were recurrent attacks of palpitation of the heart and precordial pain. She felt much better for the next few years, but in 1927 began to suffer from recurrent seizures of severe blood spitting. Since these episodes appeared about the time of her menstrual periods, little attention was paid to them at first. Their increase in frequency as well as the amounts of blood expectorated at such times became alarming, and she entered the hospital for their relief.

Physical Examination.—When first seen by us the girl appeared well-nourished and mentally alert but a bit irritable. The apical impulse of her heart was in the fifth intercostal space near the midclavicular line. The first heart sound was accentuated but partly obscured by a soft blowing systolic murmur. It was preceded by a short, rough rumbling diastolic murmur. The heart rate averaged 100 beats per minute, and the rhythm was regular. The blood pressure was 98/54. The lungs were clear. The liver and spleen were not palpable. There was no edema of the lower extremities.

The radiographic examination of the chest showed a slight increase in the lung marking due to congestion. The heart was vertical and there was marked prominence of the pulmonic artery. The electrocardiogram showed right axis deviation.

Course and Progress.—During her first stay in the hospital, between April 1, 1928, and June 20, 1928, she was afebrile and was up and about most of the time. She was readmitted on October 10, 1928, three weeks after a very severe hemoptysis for which she had been at the Lincoln Hospital. Reexamination at this time did not reveal any changes from the previous one. Comparison of the x-ray plates taken at the time of the first examination with those obtained now did not disclose any change in the lung shadow. She was sent home after a short stay and was well until June 22, 1929, when she was readmitted for a third time.

On this occasion she complained of a severe pain between the shoulder blades. This was persistent and it was frequently accompanied by palpitation of the heart severe enough to compel her to stay in bed. The first blood-spitting episode observed by us occurred on August 26, 1929. This attack started at 7:30 A.M. She complained of difficulty in breathing and palpitation of the heart. The respirations were rapid and labored. Her complexion was pale and sallow. There were large beads of perspiration on her forehead. The heart rate averaged 160 beats per minute and it was regular. The blood pressure was 110/70. Five minutes after the

onset, coughing set in, and shortly the breathing became asthmatic in type. Within ten minutes there was frothy expectoration with blood-tinged sputum. Shortly this became profuse and bright red in color, and was brought up in large quantities with each coughing spell. It became so profuse that it poured out of the nostrils. The coughing would stop for a while and then increase spasmodically when the bleeding would recur. At this time the material expectorated looked like pure blood. The frothiness had disappeared and yet there were no clots in the blood. This continued in recurrent spurts for half an hour before it ceased, leaving the girl in an exhausted condition. The asthmatic type of breathing continued for the rest of that day.

Between this day and July 13, 1930, when she died, following an unusually prolonged attack, she had ten other similar episodes, some, however, not so severe. Sometimes associated with the onset of one of these attacks, she presented evidences of somatic hallucination and delusions. She was apparently well oriented but had a tendency to fabricate. She was unquestionably psychotic, but it was difficult to state whether the psychosis was due to the onset of the acute episode or part of her cardiac disease.

Death followed a prolonged seizure of mild blood spitting which was preceded by a mental derangement that necessitated physical restraint.

Autopsy (No. 5002) performed thirty-two hours post mortem by Dr. J. J. Vorzimer. (Only the interesting findings are reported):

The heart weighed 200 grams. The pericardium was smooth and glistening and showed no abnormalities. There were a few areas of hemorrhage in the epicardium over the auricles. The epicardial fat was moderate in amount and sharply defined from the muscle. The myocardium was firm and slightly thickened. The aortic, pulmonary, and tricuspid valves showed no abnormalities. The mitral valve was of the "button-hole type" and showed fusion and thickening of the two leaflets. There were a few small, white thickenings on the auricular surface of the aortic leaflet near its edge. The papillary muscles were hypertrophied and the chordae tendineae were shortened. The coronary vessels showed no abnormalities and were patent throughout. The left auricle was somewhat dilated and hypertrophied, and there was some hypertrophy of the right ventricular wall.

The pleura was smooth and glistening over both lungs except for a few scattered areas of fine fibrin on the upper lobe. Both lungs were crepitant, except in the upper lobes which felt fleshy and firm. On section both upper lobes presented dry, dark red, homogeneous surfaces from which blood and a small amount of serum could be expressed.

The lower lobes on section showed slight edema and had pink surfaces mottled with areas of anthracosis. From these surfaces a frothy, pinkish colored serum could be expressed. The bronchi showed no abnormalities. The pulmonary vessels showed many raised yellowish plaques.

Microscopic examination of some of the lung tissue showed the pleura to be thick and congested. The alveoli were filled with red cells, desquamated epithelial cells, serum, and "heart failure" cells. The vessels showed thickening of the intima. The alveolar capillaries were tremendously congested.

Other alveoli were emphysematous and the walls of the bronchioles showed well-defined areas of lymphocytic infiltration. There was marked increase of the perivascular fibrous tissue. Several of the bronchi showed marked engorgement of the capillaries in the mucosa.

CASE 3.—History No. 20828-R. Diagnosis: C.R.C.V.D., mitral stenosis and insufficiency, paroxysmal pulmonary hemorrhages.

M. G., male, aged nineteen years, was first admitted to the Montefiore Hospital on February 2, 1932, and has been under our observation ever since. His chief

complaints on admission were repeated blood-spitting episodes, and almost constant pain in the back between the shoulder blades, and palpitation of the heart.

Previous History.—Four years prior to his admission he was advised by school physicians that he had chronic valvular heart disease. Two years later he was suddenly awakened one night with a severe coughing spell, difficulty in breathing, and palpitation of the heart. He claims that shortly after the onset of this seizure he brought up large quantities of "pure blood." With the subsidence of this episode,

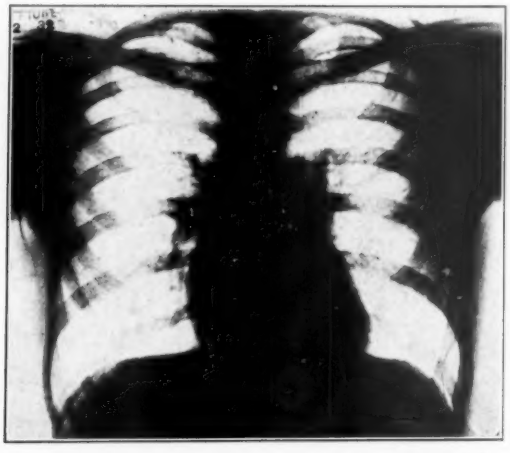

Fig. 1.—(Case 3) A roentgenogram of the chest obtained during the interval when the patient was free from symptoms. The heart shadow shows moderate rounding of the left ventricle and the lung fields are clear, with the exception of the hilar shadows which are accentuated.

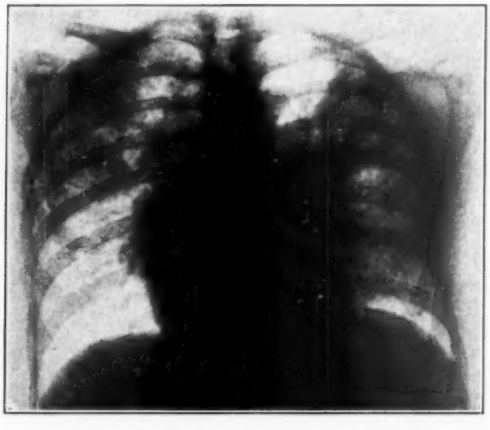

Fig. 2.—(Case 3) A roentgenogram of the chest obtained two days after the onset of a paroxysmal seizure of pulmonary hemorrhage. Note that the hilar shadows are markedly accentuated and that there is diffuse transudation within the entire right upper lobe and almost the whole of the left lung with the exception of its apex.

he developed sticking pains in the back between his shoulder blades in the region of the first four dorsal vertebrae. Incidentally, he complained of drawing pains in his legs and muscles, so that he could hardly move. Several hours later he was transferred to the Bellevue Hospital where he remained for six days, although the blood spitting disappeared twelve hours after the onset of the attack.

Eight weeks before admission to the hospital he experienced a similar episode of paroxysmal bleeding from the lungs which, however, was not severe and lasted only

one hour. Since then he has been ambulatory but has been having recurrent seizures of palpitation of the heart and occasional missed beats.

Physical Examination.—The boy appeared well-nourished. There was no evidence of any dyspnea, and his neck veins were not distended. The apical impulse of the heart was in the fifth intercostal space to the left of the midclavicular line. The first heart sound was accentuated and was partly obscured by a soft blowing systolic murmur which in turn was followed by a short rough rumbling diastolic murmur. The heart rate averaged 86 beats per minute and the rhythm was regular. The systolic blood pressure was 126 mm. of mercury and the diastolic 92 mm. of mercury. The lungs were free from moisture. The liver and spleen were not palpable, and there was no edema of the lower extremities.

Radiographic examination of the chest showed some pleural thickening in the right costophrenic angle. There was moderate haziness of the pulmonary fields. The heart was placed vertically. The pulmonic artery and conus portion of the right ventricle showed some enlargement. The left ventricle was not definitely enlarged. The electrocardiogram showed right axis deviation.

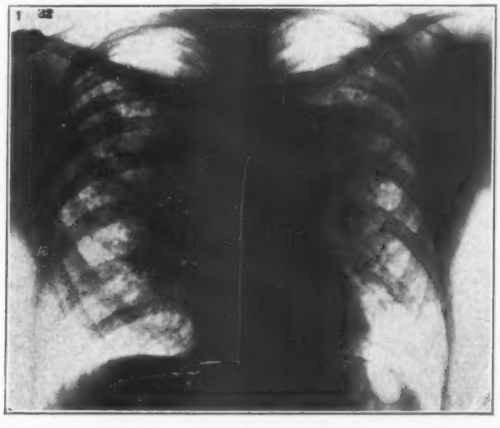

Fig. 3.—(Case 3) A roentgenogram of the chest obtained four days after the onset of a paroxysmal seizure of pulmonary hemorrhage. Note that both the bases and apices are now clear, while the root shadows are still markedly accentuated.

Course and Progress.—At 10:30 P.M., February 29, 1932, the boy began to complain of severe pain in the lower region of his spine. When seen then he appeared very apprehensive and was tossing from side to side. Soon his head was thrown backward and he assumed a position of opisthotonus. His legs, however, were extended forcibly, and he resisted any attempts at flexing them. He complained of great pains when he was touched or moved. It was necessary to restrain him because of his violence.

His face had an anxious expression and his entire body was covered with large beads of perspiration. His pupils were dilated but they reacted to light and in accommodation. His speech was incoherent and he complained that his teeth were "falling" out. By distracting his attention it was found possible to press hard over his dorsal region without eliciting any tenderness.

At midnight of this day his pulse was 80 and his respirations were normal. The lungs did not reveal any moisture, but on the following morning he was awakened after a coughing spell and then vomited a large quantity of coffee-ground material. Shortly he began to expectorate frothy, tinged sputum, and thereafter he frequently brought up quantities of bloody fluid for the next three days. At this time there

were diffuse râles over both of his chests, anteriorly and posteriorly, from the apex to the base. His temperature was elevated to 101° F., and he showed moderate increase in the leucocyte count.

An x-ray examination of the dorsal spine obtained on March 1, 1932, during this episode did not reveal any changes in the bones of his spine. Roentgen examination of the chest on this day showed dense shadows on both sides, extending from the hilum well outward toward the axillary region. The apical regions of the lungs, as well as the extreme bases on both sides, appeared clear. Three days later, when his blood spitting had ceased, the lungs were clear again and most of the shadows just described had disappeared.

In the next six months he was seen and studied during several of these attacks, each one of which was associated with an "aura" consisting of psychogenic manifestations. Apparently the boy had premonition of the onset of these attacks. He became apprehensive for several hours before their appearance. Palpitation of the heart was the first sign. His heart rate would rise from an average of 90 beats per minute to 140 beats, but the electrocardiograms invariably revealed normal sinus rhythm. The pain in the back, of which he always complained, would be augmented at these times, and the opisthotonus position which he assumed appeared to be one in which he was most comfortable at such times. Difficulty in breathing accompanied by profuse perspiration appeared after that, and then recurrent coughing spells would indicate the approach of the blood-spitting episode. At times he would talk irrationally for hours before the appearance of the lung signs, and often he would sleep through these attacks, when the vomiting of dark-ground material would point to the fact that he had had a seizure through the night and had swallowed most of the fluid. More often, frank bloody fluid would flow from both his mouth and nostrils. Peculiarly enough, the psychic disturbances would all pass away with the onset of the bloody expectoration. In between attacks he would be perfectly comfortable and at present is up and about most of the time, having been free from symptoms for about two months.

DISCUSSION

Blood spitting in one form or another has been well known to the older clinicians as a common manifestation of patients with heart disease. The French called it "hemoptosie cardiaque" or "forme hemoptoique des maladies du coeur.[1, 2] But in most instances it was only the occasional red-streaked sputum that focused the physician's attention to the underlying cardiac lesion. And in the era prior to the x-rays, it was common practice, in the absence of any definite physical signs, to eliminate a tuberculous process as the cause of the mischief by the presence of "heart failure cells" in the rusty sputum of such patients.[3] We now know that other causes of such blood spitting in patients with heart disease may be due to intrinsic disease of the lung independent of the heart lesion, such as cancer of the lung, bronchiectasis, and varices of the bronchi, to mention only a few of the conditions which we have encountered in our experience with such patients.

Severe hemorrhages, however, in the presence of mitral stenosis have been rather uncommon even with massive infarction of the lung,[4, 5, 6, 7] and for this reason the various manifestations which these patients exhibit place them in a different category from others with heart disease.

THE CLINICAL SYNDROME

The attacks for which these patients seek relief are characterized by periodically recurring seizures of blood spitting heralded at times by an aura with psychogenic manifestations; severe palpitation of the heart with a marked increase in the pulse rate; pains in the back between the shoulder blades extending down the spinal region, and difficulty in breathing accompanied by paroxysmal coughing ending at times in severe pulmonary hemorrhages.

These attacks usually appear in ambulatory young adults with mitral stenosis many years after the initial bout of rheumatic fever and may be the first evidence of the presence of heart disease. Signs of congestive heart failure are usually absent. The seizures vary in number from one to several a month, and their increase in frequency and duration is always of ominous prognostic significance. They have never been noted during an active bout of rheumatic fever, and in only one instance were they preceded and accompanied by a slight rise in temperature lasting two days.

The Psychogenic Manifestations.—Sometimes they are preceded by an aura lasting several hours before the actual attack is ushered in. There is mental anguish with a fear of something grave impending. The sensorium becomes cloudy and the speech is frequently unintelligible. Hallucinations appear, there are visual disturbances, and the patient may go through all sorts of contortions and body movements that are uncoordinated. In the absence of objective localizing neurological signs, some have been suspected of malingering, and one girl who was admitted to the neurological service of an institution was considered to be suffering from major hysteria. She died shortly after, following a severe hemoptysis and autopsy revealed a tight mitral stenosis, without any infarcts in the lung or points of bleeding from any of the pulmonary vessels. In two girls, the slight mental disturbances appearing prior to such seizures were thought to have been due to the associated menstrual changes, and in these instances the blood spitting was considered as vicarious menstruation, no consideration being given to the underlying mitral disease present. The neck rigidity and opisthotonus in one boy, a position assumed by him prior to the onset of the attacks, presumably because of the accompanying severe pain in the back, led to the diagnosis of meningitis, and he was subjected to spinal taps, with no abnormal findings, of course.

The mental disturbances become graver with the increase in the frequency and duration of these episodes, and in some patients the manic-depressive symptoms have compelled us to use physical restraint.

Skin Manifestations.—In one boy a severe generalized urticarial eruption appeared on four separate occasions several hours prior to the development of his paroxysms of coughing, and there was alternate blanch-

ing and cyanosis of several of the fingers before profuse perspiration covered the entire body. The skin eruptions disappeared within five hours.

Pains in the Back.—Sometimes the first evidence of an oncoming seizure may be a sharp pain in the back between the shoulder blades. It may be well localized for several hours, but then may radiate along the region of the spinal column as far down as the lumbar vertebrae. This pain is, as a rule, unassociated with tenderness. Only rarely have the pains been localized to any other region. In one girl they were severest in both groins in addition to the interscapular region.

Palpitation of the Heart.—Associated with these pains there is invariably palpitation of the heart. The heart rate may increase up to 150 or 170 beats per minute, and with this acceleration there is violent pulsation of the vessels of the neck. The rapid beating of the heart may persist for several days after the major syndrome has disappeared, and its return to the original level may be best appreciated by counting the night heart rate when the patient is asleep. It is at such times that the accelerator influences over the heart are in abeyance. Whereas during the seizure of asthmatic breathing with hemoptysis, the heart rate remains high even during sleep, when the attack subsides, the heart rate may be high during the waking hours but under 60 beats per minute during sleep. Irregularities in the heart rhythm have not been observed prior, during, or subsequent to any of the seizures.

Cough and Hemoptysis.—The most striking and alarming feature of these episodes is the blood spitting that appears shortly after the onset of difficulty in breathing which is ushered in at the same time as the palpitation of the heart. At first the respirations are merely increased. Within a short time the expirations become prolonged, just as in the breathing of asthmatic patients when only sibilant and sonorous râles are heard over both chests. Paroxysmal coughing with mild blood spitting usually follows, and unless the blood is brought up from the lungs with each coughing paroxysm, it may be reflexly swallowed as it spills over from the trachea into the pharynx. This has been observed to occur without the patient's knowledge during sleep. The evidence that such a seizure has taken place during a patient's sleep is obvious when irritability of the stomach follows its overflowing, and the swallowed blood from the lungs is vomited in large quantities as brownish coffee-ground material.

The first expectorated transudate from the lungs may be the frothy type of red-tinged sputum that is seen so often in patients with mild attacks of pulmonary edema, a condition which, like profuse hemoptysis, may also occur paroxysmally in patients with mitral stenosis.[8] This state may last several hours and finally end in a profuse and abundant bright red hemorrhage, varying in quantity from one hundred to several hundred cubic centimeters. Whereas "heart failure cells" are easily

seen in the expectorated material during the milder seizures, when the bleeding is abundant, only red cells and fibrin are seen on the microscopic examination. We have never observed any clots brought up with the sputum, and the streaking may stop as suddenly as it is ushered in.

With the appearance of the blood, the physical signs in the lungs change and may be very variable from hour to hour, depending upon the severity and the duration of the seizure. Dullness with diminished breath sounds may be at first localized to only one part of the chest, the upper right chest being the most common site and the most frequently involved. Later, as the attack is prolonged, the signs may extend to both lungs, anteriorly and posteriorly, and now the râles become large, moist, and bubbling, and appear very near to the ear.

On only one occasion was there noted a temperature increase to 101° F., and this lasted for two days. Localized friction sounds, such as are heard so frequently in infarction of the lung with pleural involvement, are absent, as is the localized sharp pain which often accompanies the development of these.

The X-ray Signs.—The usual roentgen ray findings in the average patient with moisture in the lungs is well known.[9] Stasis in the lungs is characterized by an increase in the hilar shadows, which in the presence of mitral stenosis assumes the form of a capital H with both limbs of the H extending upward and downward from the root of the lung toward the periphery. In some there is an increase in the density of perivascular tissues, and in the further advanced cases the lungs have the mottled appearance seen so frequently in miliary tuberculosis. Often there is thickening of the pleura from some previous inflammation which is seen on the films as darker shadows along the edges of the lungs; and occasionally a still denser shadow at the bases, in particular at the left base, has been found associated with atelectasis from compression of the bronchus by an enlarged left auricle. In addition to such signs there may be superimposed upon the lung fields of patients with blood-spitting episodes, diffuse shadows extending from the hilum toward the periphery, often mistaken for infiltrations within lung parenchyma due to pneumonia. The transudates in the alveoli may be localized, at such times, to only one part of the lung field, often restricting themselves to one lobe, and may remain so until the end of the attack. These shadows have also been mistaken for localized interlobar effusions when the exudate involved the areas adjacent to the interlobar fissure. All of these shadows have been seen to disappear within a few days after their development without leaving any traces in the lung fields to indicate the widespread involvement observed previously.

The most common differential diagnosis in which the x-ray shadows may shed some light on the underlying pathological lesion responsible for blood spitting is that of infarction of the lung, in which a wedge-

shaped density is often found to spread from the hilar region toward the periphery, well demarcated from the rest of the lung tissue. In such cases, however, the clinical manifestations of pain, fever, leucocytosis, and jaundice are often more reliable than the roentgen ray evidence.

Treatment.—It has been impossible to prevent the onset of such seizures in any of our patients. Once the attack sets in, the adequate use of morphine sulphate as a sedative, with repeated injections of atropine sulphate, has helped to dry up the secretions and allay the apprehension that is always present. With all this, however, death has taken place from asphyxia when the attack has been very severe, although we have not observed death to occur in the actual process of the hemorrhage.*

Pathology and Pathogenesis.—Very recently an attempt has been made by Proft[7] on the basis of very meager pathological findings, to separate patients with heart disease and severe hemoptyses into two distinct groups. In the first, in which no bleeding point is found within the lung parenchyma or its vessels, the hemorrhage is considered the result of the sudden dilatation of the lung capillaries with diapedesis in the alveoli. Although such patients have heart failure cells in their sputum, peripheral manifestations of congestive heart failure, such as hepatic enlargement and anasarca, are usually absent. In the second group with peripheral stasis, Proft attributes the bleeding to marked dilatation of the capillaries lining the small bronchioles and the possibility of rhexis or rupture of these is held to account for the symptoms and signs that follow.

Our own pathological observations have revealed the lungs following such hemorrhages to be large, fleshy, and firm. On squeezing them, blood could be easily expressed. The cut sections were red and homogeneous. The bronchi and trachea showed marked engorgement and the alveolar capillaries were tremendously congested. No ruptured vessels were seen either grossly or microscopically in many sections obtained from these lungs. In the absence of any embolic or thrombotic manifestations, the most plausible cause for the bleeding at present seems to be that of diapedesis. The immediate factors responsible for initiating this mechanism periodically in recurring forms in such patients as we have described above merits further attention and study.

SUMMARY AND CONCLUSIONS

1. Severe paroxysmal pulmonary hemorrhages, not due to intrinsic disease of the lungs, are uncommon in patients with mitral stenosis. Three cases are reported of young adults under thirty years of age, suffering from chronic rheumatic cardiovalvular disease with mitral

*The prognosis in the few cases we have observed has been poor, as most of the cases have died within a few years of the onset of the hemoptyses. One boy is still living a little over two years after the appearance of such attacks.

stenosis, whose main presenting symptoms were recurrent attacks of pulmonary hemorrhages.

2. These attacks were characterized at times by an "aura" with psychogenic manifestations, severe pains between the shoulder blades, and palpitation of the heart. In one patient an urticarial rash ushered in the seizures.

3. The onset of these attacks was usually during an afebrile period and came on many years after the first evidence of rheumatic fever.

4. The attacks themselves were characterized by dyspnea, pain, asthmatic breathing, cough, and hemoptysis. At first the expectoration was frothy in nature, but later there were frank hemoptyses in quantities of from one to several hundred cubic centimeters of blood.

5. The lungs during such seizures showed evidences of either localized or diffuse transudation in the alveoli, and there was a characteristic x-ray picture that was often mistaken for pneumonia. The attacks would last from one hour to several days, and with their cessation the lung signs cleared up entirely.

6. It was impossible to prevent the onset of such seizures in these patients by any medication. Morphine sulphate and atropine sulphate administered in adequate doses following the seizures seemed to allay the fear and abate the hemoptysis.

7. Two of these patients died within three years following the onset of such recurrent episodes. In the one case with autopsy no bleeding point could be found.

8. It is probable that in the absence of any embolic or thrombotic manifestations in the lungs, such seizures are the result of some reflex stimulation of the capillaries lining the alveoli, resulting in hemorrhages from diapedesis, or possibly also from rhexis of capillaries lining the walls of the bronchial tree.

(*For discussion see p.* 113.)

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A CLINICAL CONCEPTION OF RHEUMATIC HEART DISEASE*

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MOST physicians are still of the opinion that the cause of rheumatic fever or rheumatic heart disease is unknown. It is true that of all infectious agents the streptococci have been studied most arduously and that they are apparently more intimately related to rheumatic fever and its various accompaniments, than other microorganisms. Despite these painstaking bacteriological efforts, on critical analysis it cannot be said that streptococci cause rheumatic heart disease; however, such infections may aggravate the rheumatic condition. Similarly, one may say that the diligent search and removal of foci of infection has proved far from effective either in preventing or in ameliorating the terrible ravages of the disease. With the situation as it stands, recognizing the great importance of continued study of the bacteriological aspects of the question, there is another phase of the problem that I feel has not received sufficient attention. I refer to the condition of the host or patient, the internal environment in which the disease develops, and especially the possible rôle the glands of internal secretion may be playing.

The response of the human body to outside influences is very variable and difficult to predict. This is true whether the offending agent is a physical, chemical, or infectious cause, or whether it is a psychic trauma. It is common knowledge that one individual may lose his entire business and as a result commit suicide, while another merely smiles and starts right over again. One jilted suitor becomes depressed, another takes to drink and a third laughs it off. So it is with infectious diseases. A luetic infection develops into a stubborn dermatological syphilide in one case and in another may show very little skin and a great deal of early nervous system involvement, as if the infection had taken a direct route to the brain and meninges. We have been too ready to ascribe these differences to variations in the virulence or specific type of the invading organisms. On the other hand, there is much to make us believe that the peculiarity of the patient may have a great deal to do with these inexplicable phenomena. Not only do human individuals differ from each other, but we differ from year to year and from month to month in our bodily behavior, in our physical, anatomical, and chemical make-up, and presumably in our biological reactions to bacteriological invasions. Some extremely important observations in this regard were published by Brown[1] and his coworkers. He found that in rabbits there were con-

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siderable differences in the relative weight of the different organs of the body during different months of the year. This was particularly true of the endocrine glands. It is reasonable to assume that similar seasonal variations occur in human beings. By this is meant that we have a greater or lesser amount of thyroid or pituitary gland in proportion to the entire body weight at one time of the year than at another. Similar changes in the chemical constituents of the blood, such as calcium, phosphorus, lecithin, and cholesterol, were also observed. The purpose of this communication is to call attention to the possibility that such changes in balance in the internal environment of the human body may have a direct bearing on the problem of rheumatic fever.

The causative agent of rheumatic fever is probably very prevalent in certain parts of the world. Notwithstanding this great prevalence and the failure to develop lasting immunity to recurrences (for the very opposite is characteristic of the disease), only a small part of the population develops this disease. It seems likely that many if not all are exposed to the infection, certainly if the streptococci have much to do with it. Is it not reasonable to assume that the condition of the individual host determines whether the disease develops and what form it will take? One child gets the infection and manifests it in the form of St. Vitus' dance, another polyarticular rheumatism, a third skin lesions, a fourth may show none of these lesions and respond purely with a pericarditis, and a fifth may only have a slight fever, sweats, and anemia without gross cardiac or arthritic involvement. Furthermore, in the same person the internal environment may be in such a state that during one month or one year he may have chorea and at another rheumatism. Such variations I do not believe can be ascribed to changes in the infectious agent but are more likely due to changes in the host.

A very striking observation with regard to chorea illustrates the general thesis presented above. Whereas chorea very commonly lasts for months and tends to recur at times over a period of years, one practically never sees chorea in patients over twenty years old, except under one circumstance and that is in a pregnant woman. Here again pregnancy fundamentally alters the internal environment of the patient, especially the endocrine balance. It is more reasonable to assume that this altered state of the internal environment is responsible for the peculiar recurrence of this disease at this time, than to suppose that the infectious agent just happened to become reactivated during pregnancy. A further illustration is the occurrence of so-called "growing pains." We all frequently see these children with recurrent pains in the limbs during their early years, which disappear as full growth is established. The term "growing pains" attains more than colloquial significance when it is viewed in the light that the rheumatic pains disappear and the dis-

ease is held in check when the proper endocrine balance, possibly determined in this instance by the pituitary gland, has been established.

Another peculiarity of rheumatic fever is of interest in relation to the internal environment of the host, i.e., the familial incidence of the disease. It is obvious that children of the same family are exposed to the same surroundings—food, climate, and hygienic conditions. These factors and the spread of infection by contact no doubt are important in producing a high familial incidence of the disease. I do not think, however, that this is the entire explanation. There must be an additional hereditary factor of vascular vulnerability. The following experiences throw some light on this question. A husband and wife died of coronary artery disease. Among their children three developed hypertension in the thirties or early forties. In each instance there has already been one child (a grandchild of the original anginal grandparents), with rheumatic fever or chorea. These three rheumatic children have lived in entirely different localities, one in New Hampshire and the other two in different parts of Massachusetts, and see each other but rarely. It hardly seems that contact or environment are adequate to explain this. Likewise, a little boy, eight years old, previously perfectly well, developed chorea during the month of February. His mother, a most intelligent person, mentioned as a curious fact that her brother about twenty-five years previously had had the same disease (chorea) at the same age (eight), and at the same month of the year (February). It is unlikely that these four variables, disease, age, month, and family should occur together by mere chance. In the light of the work of Brown previously mentioned, it is probable that the endocrine or biological state of that boy, which he inherited from his mother, was just appropriate at that time to develop the disease just as happened to his uncle. These and similar experiences form a background that is not at all new but which deserves more intensive consideration and emphasizes the importance of the host in the development of rheumatic heart disease. The problem lends itself somewhat to experimentation inasmuch as the progress in endocrinology has been considerable during the past decade. At present numerous hormones of the glands of internal secretion are available, so that the effects of either an increase or decrease in their functions may be studied in relation to the susceptibility to disease. There is reason to hope that such investigation will prove fruitful in throwing light on methods of prevention and treatment of rheumatic heart disease.

(*For discussion see p.* 112.)

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RHEUMATIC MANIFESTATIONS IN SUBACUTE BACTERIAL ENDOCARDITIS IN CHILDREN*

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A POSSIBLE relationship of subacute bacterial endocarditis to rheumatic fever† has long attracted the attention of workers in this field. At present, some believe that these two conditions are different diseases and others that they are merely different manifestations of the same disease. Since subacute bacterial endocarditis and rheumatic fever are not infrequently closely associated, a clinico-pathological study of the two diseases, when occurring in the same individual, seemed to offer a method of investigation which might aid in a better understanding of their possible relationship.

It is sometimes difficult to make a differential diagnosis between rheumatic fever and subacute bacterial endocarditis. At times the clinical picture of the former merges almost imperceptibly into that of the latter. As a rule, however, there are certain essential differences. In rheumatic fever, endocarditis is but one manifestation of a general process, while in subacute bacterial endocarditis the valvular infection is the essential seat of the disease. It has been noted that rheumatic fever occurs chiefly in the first two decades of life while subacute bacterial endocarditis occurs more often after the second decade (Thayer[3]). It has been said repeatedly that subacute bacterial endocarditis rarely occurs in patients with mitral stenosis or auricular fibrillation (Rothschild et al.,[4] and Levine[5]) which are among the common manifestations of rheumatic heart disease. It is known that subacute bacterial endocarditis at times develops long after the clinical evidence of an active rheumatic infection has subsided. Finally, the etiology of rheumatic fever is unknown, while *Streptococcus viridans* is usually demonstrable in blood cultures taken from patients with subacute bacterial endocarditis. In spite of such apparent differences which can be recognized clinically, it is generally emphasized that a heart valve which has been the seat of rheumatic endocarditis may later become involved in subacute bacterial endocarditis.

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†We fully realize the inadequacy of the terms rheumatic fever, rheumatic infection, rheumatic arthritis, etc. But because the more recently used terms, such as rheumatismus infectiosus specificus (Gräff[1]), rheumatic granulomatosis (Fahr[2]), etc., also do not express the essential of what is generally known as rheumatic fever, we decided to use the old terminology which at least has the advantage of more common usage.

TABLE I

NO.	AGE	SEX	HISTORY OF PREVIOUS RHEUMATIC INFECTION	NUMBER OF RECURRENCES	TIME INTERVAL BETWEEN RECURRENCES	TIME INTERVAL FROM LAST RHEUMATIC MANIFESTATION TO ONSET OF SUBACUTE BAC. END.	HISTORY OF PREVIOUS HEART INVOLVEMENT	DURATION OF LIFE	CAN ONSET OF S.B.E. BE DIFFERENTIATED FROM LAST RHEUMATIC INFECTION
1	10 yr.	M	Acute polyarthritis	3	Varied from 1 to 1½ yr.	5 mo.	Yes	3 yr.	No
2	13 yr.	M	Acute polyarthritis Joint and muscle pains	Repeated	Varied from 4½ yr. to 4-5 wk.	2 wk.	Yes	7 yr.	No
3	5½ yr.	M	Acute polyarthritis Sore throats	1		5 mo.	Yes	1½ yr.	Yes
4	17 yr.	M	Acute polyarthritis Fleeting pains	Repeated	Varied from 4 yr. to 6 mo.	7 mo.	Yes	6½ yr.	Yes
5	19 yr.	F	Acute polyarthritis	2	9½ yr.	3 mo.	Yes	10 yr.	No
6	19 yr.	F	Acute polyarthritis	1		10½ yr.	Yes	11 yr.	Yes
7	5 yr.	M	Swollen joints following acute infection	1		4 wk.	No	4 wk.	No
8	13 yr.	M	Sore throats Fleeting joint pains	Repeated	Varied from few wk. to several mo.	2 wk.	No	Age of onset unknown	No

TABLE I—CONT'D

NO.	AGE	SEX	HISTORY OF PREVIOUS RHEUMATIC INFECTION	NUMBER OF RECURRENCES	TIME INTERVAL BETWEEN RECURRENCES	TIME INTERVAL FROM LAST RHEUMATIC MANIFESTATION TO ONSET OF SUBACUTE BAC. END.	HISTORY OF PREVIOUS HEART INVOLVEMENT	DURATION OF LIFE	CAN ONSET OF S.B.E. BE DIFFERENTIATED FROM LAST RHEUMATIC INFECTION
9	11 yr.	F	Sore throats	Repeated	Varied from 3-6 mo.	5 yr.	Yes	8 yr.	Yes
10	14 yr.	F	Sore throats Fleeting joint pains	Repeated	Varied from few wk. to several mo.	Unknown	No	Age of onset unknown	Yes
Summary			In all cases	3 cases had 1 attack, 1 case had 2 attacks, 1 case had 3 attacks, 5 cases had repeated attacks	Few weeks to 9½ yr.	2 wk. to 10½ yr.	In 7 cases	4 wk. to 11 yr.	5 yes 5 no
10 rheumatic cases			In 9 cases	3 cases had 1 attack, 3 cases had 2 attacks, 3 cases had repeated attacks	Few weeks to 7 yr.	2 wk. to 3 yr.	In all cases	2 mo. to 9½ yr.	

Up to the present time, most of the observations on a relation between subacute bacterial endocarditis and rheumatic fever have been made in adults. This is probably due to the fact that until a few years ago subacute bacterial endocarditis in children was thought to be extremely rare (Blumer[6]). In adults, a rheumatic infection may antedate by a long period of time the death which results from subacute bacterial endocarditis. Consequently, any association between these two conditions may have become obscured.

We selected for study cases of subacute bacterial endocarditis occurring in children. A study of the clinical histories of these children, together with gross and histological examinations of the hearts, was undertaken in order to see if there existed evidence of a preceding or coincident rheumatic infection, and, if so, whether any relationship between the two diseases could be established. In children the time interval between a possible rheumatic infection and the subacute bacterial endocarditis would necessarily be shorter than in adults.

Our series comprises 10 cases of subacute bacterial endocarditis. Eight were children and 2 in the early adolescent period who had been under observation since childhood.* The clinical diagnosis of subacute bacterial endocarditis was confirmed in each case at autopsy. Six of this group were males and 4 were females; the ages ranged from five years to the young adolescents, both of whom were nineteen years old. In 6 of the 10 patients we were able to obtain a clear-cut history of a preceding rheumatic polyarthritis; 3 other patients gave a history of frequent sore throats and fleeting joint pains which might be interpreted as evidence of a rheumatic infection. In another patient there was a history of transient joint swellings following an acute infection, diagnosed as measles. None of the children gave a history of chorea, and subcutaneous nodules were present in only one patient. Table I gives a summary of the significant clinical findings of our patients. It also summarizes the comparable clinical findings in 10 other children dying of rheumatic heart disease, used as controls.

Of the 6 patients with a definite history of previous rheumatic polyarthritis, 2 had only one attack, 1 had two, 1 three, and 2 others had repeated attacks. Of the 2 patients with only one attack, the time interval between the rheumatic polyarthritis and the appearance of clinical signs of subacute bacterial endocarditis was five months in one and nine and one-half years in the other. In the 2 patients who had two and three attacks of polyarthritis, the time interval between the last attack and the clinical onset of subacute bacterial endocarditis was three months and five months respectively. Of the 2 patients who had repeated attacks of polyarthritis, the last attack antedated the clinical

*We are indebted to the Attending Staff of the Sarah Morris Hospital for the use of these cases.

picture of subacute bacterial endocarditis by seven months in one, while the other had an acute polyarthritis two weeks before the clinical signs of subacute bacterial endocarditis appeared. Of the 4 patients who did not have a definite history of rheumatic polyarthritis, 1 revealed clinical evidence of subacute bacterial endocarditis five years after the occurrence of the last probable clinical rheumatic manifestation, 1 developed acute polyarthritis shortly after admission to the hospital and four weeks later the first clinical signs of subacute bacterial endocarditis appeared, another had transient joint swellings three weeks before the appearance of the clinical signs of subacute bacterial endocarditis and in the remaining patient, no time relationship could be established and clinical evidence of bacterial endocarditis developed after a long period of time during which the patient was apparently well. In the 7 patients who had more than one attack of a clinically active rheumatic infection, the time between the attacks varied greatly. Five of these 7 patients had repeated attacks at intervals varying from a few weeks to several months. In 2 of these patients, there had been an interval of four years during which time there was apparently no clinically active rheumatic infection. In the 2 cases with two and three attacks respectively the time between the attacks was nine and one-half years in the first instance and one to one and one-half years in the latter. In 5 of the 9 patients in whom the time interval between the last rheumatic manifestations and the appearance of clinical signs of subacute bacterial endocarditis could be estimated, the actual onset of the subacute bacterial endocarditis could not be determined. The onset of the final illness was similar in every respect to the preceding attacks of acute rheumatic infection and gradually merged into the clinical picture of subacute bacterial endocarditis. The duration of life from the first clinical evidence of an active rheumatic infection varied from four weeks to eleven years.

Eight of our patients had had previous tonsillectomies. In 6 of these the tonsils had been removed from one to seven years prior to the onset of clinical evidence of a rheumatic infection. In 2 patients tonsillectomies had been done one year and five months respectively after the onset of the first attack of acute polyarthritis. Of these 2, 1 had repeated attacks of acute polyarthritis after tonsillectomy while the other had only one attack. Tonsillectomy seemed to have no bearing in our cases on the development of a clinically active rheumatic infection or on the development of subacute bacterial endocarditis.

In 7 of our patients, the rheumatic infection was known to have involved the heart, while in 3, heart disease was first noted on admission to the hospital. Clinically, the mitral valve alone was thought to be involved in 4 instances, and the mitral and aortic valves in the remaining 6. *Streptococcus viridans* was obtained in blood cultures taken from all 10 patients.

From an analysis of the clinical records of these patients it seems evident that neither the number of preceding rheumatic attacks, the time interval between the attacks, nor the length of time elapsing from the last clinical manifestation of an active rheumatic infection to the clinical onset of subacute bacterial endocarditis is of any special significance in regard to the development of subacute bacterial endocarditis.

For comparison we analyzed the clinical records of 10 other children dying of uncomplicated rheumatic heart disease. The diagnosis in each instance was verified at autopsy. In this group, 9 gave a history of a preceding rheumatic infection. Three had one attack, 1 two, 1 three, and 5 had repeated attacks. The time between the attacks varied from two weeks to seven years. The time interval from the last evidence of an active rheumatic infection to the onset of the final illness varied

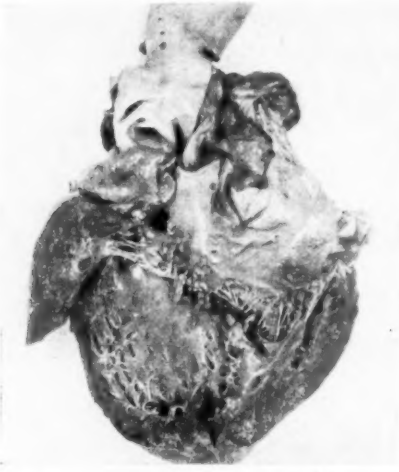

Fig. 1.—Subacute bacterial endocarditis of the mitral valve. Note the size of the vegetations, the involvement of the auricular endocardium, and the thickened chordae tendineae.

from two weeks to three years. The duration of life from the first evidence of an active rheumatic infection varied from two months to nine and one-half years. It is obvious that the number of rheumatic attacks, the interval between attacks, the time elapsing from the last attack to the onset of the final illness, and the duration of life are similar in those children studied who have had a rheumatic infection and finally developed subacute bacterial endocarditis and in those who subsequently died of uncomplicated rheumatic heart disease.

An autopsy was performed in all of our 10 cases of subacute bacterial endocarditis. These hearts showed the typical lesions of subacute bacterial endocarditis. In addition to large vegetations on the valves and the mural endocardium, various degrees of thickening were found in the valvular areas. Without giving a detailed description of the gross heart

findings, it can be stated briefly that the mitral valve alone was affected in 4 instances and the aortic and mitral valves together in 4. In one instance, the mitral and tricuspid valves were involved and in another the mitral, aortic, and pulmonic valves. In four of the ten hearts, there was evidence of moderate stenosis of the mitral orifice. Sections of the vegetations on the valves showed gram-positive cocci in every instance.

The histological examinations of the myocardium revealed various changes. Small abscesses were found in some of the hearts. In others, there were accumulations of lymphocytes and endothelial cells, partly within the parenchyma and partly within the interstitial tissue. In some instances, large areas consisting of a proliferation of connective

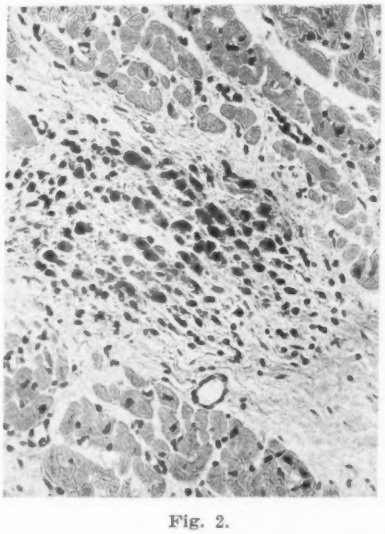

Fig. 2.

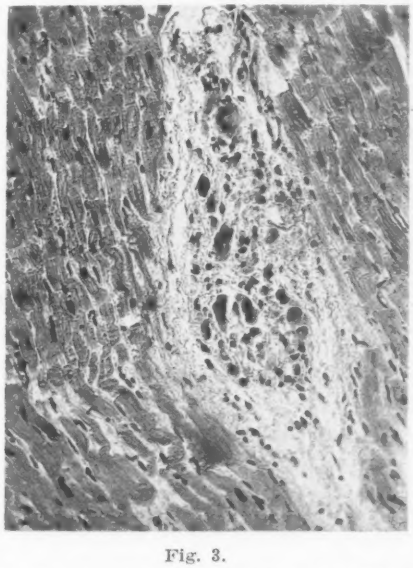

Fig. 3.

Fig. 2.—Aschoff body in the myocardium.* (Hematoxylin-eosin preparation) (×350).
Fig. 3.—Aschoff body in the myocardium. Note the multinucleated cells. (Iron-hematoxylin preparation) (×450).

tissue cells were seen, with a few newly formed connective tissue fibers, small blood vessels, and occasional lymphocytes. These areas were found interrupting the course of the heart muscle fibers. Simple fibrosis, perivascular in distribution, was often encountered.

In addition to these changes, typical Aschoff bodies were found in every instance. We wish to emphasize that whenever there was doubt whether or not a lesion was an Aschoff body, it was not diagnosed as such. Gross[7] has recently taken a similar attitude. Cellular infiltrations resembling Aschoff bodies were not included. The Aschoff bodies

*Compare Figs. 2 and 3 with Figs. 4, 5, 6, and 7, and note the morphological differences between typical Aschoff bodies and experimentally produced nodules, subcutaneous rheumatic nodules, etc.

invariably consisted of infiltrations of large cells often showing a basophilic cytoplasm containing one, two, or three nuclei, a few lymphocytes, and an occasional plasma cell and polymorphonuclear leucocyte. These accumulations of cells were almost always found in the vicinity of the blood vessels. Occasionally, necrotic foci or a fibrin-like material were encountered in these areas. The large cells were seen in parallel rows, often assuming a typical palisade arrangement. The internal structure of the nuclei of some of these cells could be compared with that of a spider web. Apparently depending upon the pressure of the surrounding tissues, the cells were either compactly arranged, the Aschoff bodies presenting an elongated appearance, or the cells were well separated from one another, the Aschoff bodies appearing rather square or round. Since a discussion of the origin of the large cells would far exceed the scope of this communication, we merely wish to state that we believe that these cells are polyblasts rather than myocytes. The various routine stains for bacteria did not reveal microorganisms within the Aschoff bodies.

We are well aware of the discrepancy of opinion as to what constitutes an Aschoff body. This was brought forward at the relevant discussion during the conventions of the Association of the American Pathologists and Bacteriologists in 1929 and 1930. This discrepancy of opinion is due to differences in the criteria used for identifying Aschoff bodies. These variations in criteria apparently result from the fact that some authors (Klinge,[8] Klinge and Vaubel[9]) believe that an Aschoff body may undergo changes and various stages of development, losing some characteristics and gaining others. We must emphasize, however, that in our opinion, the Aschoff body is unquestionably recognizable in one stage only. This is the one we have described. Structures, presumably Aschoff bodies in different stages of development, if they occur at all, should be classified under the broader term of "structures resembling Aschoff bodies." We fully realize that we may fail to recognize some Aschoff bodies, and thus fail to make a diagnosis of rheumatic myocarditis, if we use such rigid criteria for identification. On the other hand, we will be less likely to err in considering cellular infiltrations resembling Aschoff bodies as true Aschoff bodies. The accompanying pictures are characteristic, and only when the cellular infiltration conforms to such a picture do we believe we are justified in designating the structure an Aschoff body. It may be of interest to quote Thayer[10] who stated, "The focal perivascular Aschoff bodies are quite characteristic and unlike anything that we have seen under other circumstances. They appear to be distinctive of acute rheumatic heart disease."

It may be added that it is sometimes difficult to determine whether some authors consider rheumatic nodules, and Aschoff bodies in the myocardium identical or different structures. Clawson[11] uses these terms

interchangeably, and Sacks[12] stated, "Pathologists are generally agreed upon the fundamental histological similarity between the subcutaneous rheumatic nodules and the Aschoff bodies." From our experience, however, we have come to the conclusion that the Aschoff body found in the heart and occasionally in other tissues, and the rheumatic nodules found in the subcutaneous tissue, are morphologically different structures. The latter is a nonspecific tissue inflammation somewhat resembling Aschoff bodies, the former—as will be pointed out later—is more likely a specific tissue reaction. To avoid any confusion we have used the term Aschoff body exclusively for the specific lesion found in the myocardium.

So far, we have been able to show that in 8 children and 2 in the adolescent period dying of subacute bacterial endocarditis, clinical evidence of a preceding rheumatic infection was present in every instance. All cases at autopsy revealed typical Aschoff bodies within the myocardium and valvular changes characteristic of subacute bacterial endocarditis.

DISCUSSION

It seems to us that there are three possible explanations for these two findings: (1) A coincidental occurrence. (2) Both conditions may be manifestations of the same disease, differing only in the immunological response of the individual. (3) Both conditions may be related so far as the injury due to a previous rheumatic infection may predispose the valve to a subsequent subacute bacterial endocarditis.

Regardless of the possible theories of a cause and effect relation between rheumatic fever and subacute bacterial endocarditis, a coincidental occurrence cannot be ruled out. We have no proof for the assumption that rheumatic fever and subacute bacterial endocarditis may run a parallel course in the same patient without any causative relation to one another. Neither can we conclusively disprove a coincidental occurrence. We can merely say that such a coincidence seems to us quite unlikely.

Allergy is an attractive explanation of rheumatic fever and subacute bacterial endocarditis; but at best it is an hypothesis founded on animal experiments and theories which still remain to be proved. Swift[13] stated that the experimental demonstration of the hypersensitive and immune types of reaction toward streptococci seems transferable by analogy to the clinical conditions of patients with rheumatic fever and with subacute streptococcus endocarditis respectively. The difference in the diseases is supposed to lie in the difference of the reaction of the host.

Since rheumatic fever has been considered an allergic phenomenon, the significance of the Aschoff body has aroused much discussion among the workers in this field. Some still believe in the specificity of the Aschoff body, while others deny this and regard it merely as a nonspecific (hyperergic) reaction. It seems clear to us that the supporters

of the allergic theory must dispose of the Aschoff body as the specific histological entity of rheumatic myocarditis. Otherwise, they cannot assume that the Aschoff body merely signifies an hyperergic reaction of the patient toward a nonspecific cause. It must be postulated, however, that in order to disprove the specificity of the Aschoff body, unquestionable Aschoff bodies must be produced experimentally. Although it is claimed by some authors that they have been able to produce Aschoff bodies experimentally in previously sensitized animals and in others not sensitized, in our opinion this has not yet been accomplished. To judge from the reproductions of the histological sections shown by these various authors, it should be pointed out that the experimentally produced inflammatory exudate, though morphologically resembling an Aschoff body, is in no instance typical of one. We firmly agree with Aschoff[14] who, during a discussion of this subject in 1925, stated that the lesions

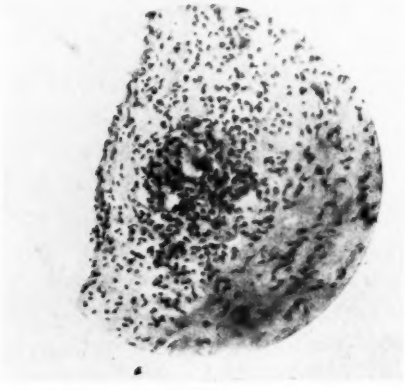

Fig. 4.

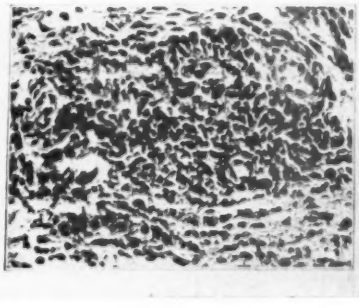

Fig. 5.

Fig. 4.—Picture taken from Klinge and Vaubel's article.[9] Called: Typical Aschoff body with giant cells in intima of aorta.

Fig. 5.—Picture taken from Swift's article.[13] Called: Subcutaneous rheumatic nodule showing intense proliferation of fixed cells around groups of blood vessels.

in question are beautiful examples of hyperergic inflammation but are not typical of Aschoff bodies. Four years later, Aschoff[15] again warned against considering the histological changes found in instances of anaphylactic shock analogous to the nodules seen in rheumatic fever. It should also be mentioned that the few reports of the presence of Aschoff bodies in the hearts of patients dying from diseases other than rheumatic fever are used as further evidence against the specificity of the Aschoff body (Siegmund,[16] Clawson,[11] v. Müller[17]). It still remains to be proved, however, whether these lesions were Aschoff bodies and, if so, whether the patients had not had a previous rheumatic infection and the Aschoff nodules were anatomical evidence of a rheumatic myocarditis. A similar criticism was made recently by Fahr.[18] It might be of interest to mention in this connection that recently Loewe, Gross and

Eliasoph[19] failed in their attempts to reproduce rheumatic disease in animals. As long as the cause of rheumatic fever is not definitely established, as long as typical Aschoff bodies are not demonstrable in conditions other than rheumatic fever, and as long as typical Aschoff bodies similar to those found in human hearts cannot be reproduced experimentally, so long must we regard the Aschoff body—just as we regard the tubercle and gumma as the specific tissue reaction toward the tubercle bacillus and the *Treponema pallidum* respectively—as a specific tissue reaction toward the unknown causative agent of rheumatic fever. We feel that at the present time we are forced to believe that the Aschoff body is a specific granuloma caused by the virus of rheumatic fever, even though it is not yet possible to demonstrate that virus by the use of present-day laboratory facilities. It seems to us that the burden of proof rests upon those who hold that the Aschoff body is the nonspecific reaction of a sensitized tissue toward a nonspecific virus.

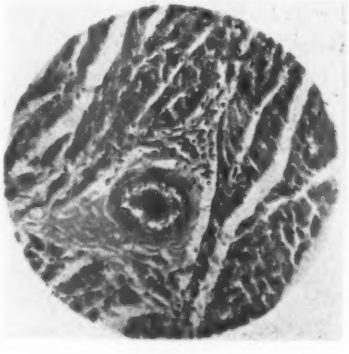

Fig. 6.

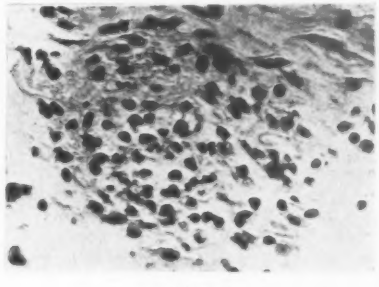

Fig. 7.

Fig. 6.—Picture taken from Klinge's article.[25] Called: Granuloma in myocardium in experimentally produced chronic recurrent anaphylactic inflammation.

Fig. 7.—Picture taken from Clawson's article.[26] Experimental nodule in subcutaneous tissue of rabbit.

The supposed immune response in subacute bacterial endocarditis as evidenced by skin tests is open to question. Howell and Corrigan[20] made skin tests on two patients with subacute bacterial endocarditis. They found the skin tests repeatedly negative in one patient, revealing an immune reaction, while in the other the tests were repeatedly positive. Both cases, as proved by post-mortem examination, were definite examples of subacute bacterial endocarditis. In both instances *Streptococcus viridans* was cultured from the blood and in both instances the skin tests were made with filtrates of these and other bacteria. As this experiment was repeated several times, it seems to show that subacute bacterial endocarditis was not an immune response in at least one of these patients. Since the hypothesis of the immune reaction does not hold in all instances, we do not believe its validity is established.

The finding of typical Aschoff bodies in the myocardium in our 10 cases of subacute bacterial endocarditis seems to us evidence against the assumption that subacute bacterial endocarditis is the immune response in a previously hypersensitive person. It would be difficult to explain why a person should react almost simultaneously in two ways; namely, with a hypersensitive reaction, of which the Aschoff body is supposed to be an example, and with an immune reaction, of which subacute bacterial endocarditis is a paradigm.

The finding of moderate stenosis of the mitral orifice in 4 of our 10 patients is of interest. It has been suggested (Fulton and Levine[21]) that the infrequency of subacute bacterial endocarditis in patients with mitral stenosis is due to the fact that the stenosis results from a progressive rheumatic infection, and consequently there is a persistence of the allergic state. Even in this small group of cases, it appears that the occurrence of subacute bacterial endocarditis in patients with stenosis of the mitral orifice is not as infrequent as one may be led to believe. Very recently, Davis and Weiss[22] in an analysis of 47 autopsies on patients dying of subacute bacterial endocarditis found stenosis of the mitral orifice in 12 instances, while in a group of 474 patients showing evidence of rheumatic heart disease this lesion was present 142 times. They concluded that subacute bacterial endocarditis occurs in about the same proportion of patients with mitral stenosis as mitral stenosis occurs in patients with rheumatic endocarditis. They also stated that statistical analysis and morphological findings indicate that any degree of rheumatic endocarditis is equally liable to be the basis of a subacute bacterial endocarditic process. Owing to the relatively large number of rheumatic hearts with mild lesions, instances of subacute bacterial endocarditis occurring with marked mitral stenosis are correspondingly infrequent. The relative infrequency of subacute bacterial endocarditis in patients developing auricular fibrillation might also be explained on this basis.

If we consider a coincidental occurrence or a difference in the immunologic response of a person as unsatisfactory explanations of the relationship between rheumatic fever and subacute bacterial endocarditis, we must then come to the conclusion that a primarily diseased valve mechanically predisposes to a subsequent subacute bacterial infection. This was the prevailing opinion until a few years ago. The most common predisposing factors were thought to be an old rheumatic endocarditis and congenital anomalies of the heart.

The congenital anomalies *per se* were generally considered to form the basis for a subsequent subacute bacterial endocarditis. It may be mentioned in this connection that we have studied 3 cases of subacute bacterial endocarditis superimposed on congenital defects of the heart. No evidence of a preceding rheumatic infection could be elicited from

the history and a careful histological examination of the hearts did not reveal any changes in the valves that could have been interpreted as evidence of a healed endocarditis. The myocardium showed neither Aschoff bodies nor fibrotic changes. It seems obvious that in these three instances the malformation alone predisposed the valves to the subsequent subacute bacterial endocarditis which was similar in every respect to the subacute bacterial endocarditis engrafted upon old inflammatory valvular lesions.

The infrequent association of subacute bacterial endocarditis and insufficiency of the aortic valve due to syphilis (Blumer[6]) is often used as an argument against the susceptibility of primarily diseased valves to subacute bacterial endocarditis. It should be pointed out, however, that the deformity of the aortic valve resulting from any type of endocarditis except that brought about by syphilis, is characterized either by a shortening of the cusps in their longitudinal diameter (insufficiency of the valve) or by adhesions between the lateral portions of the cusps (stenosis of the aortic orifice). In both conditions, we believe that the disfiguration of the valves provides, during their physiological activity, larger areas than normal for the settling of bacteria. A similar condition is found in the most frequent congenital anomaly of the aortic valve which shows a common curtain of two cusps with a slight separation in the region of the sinus of Valsalva (bicuspid aortic valve). The aortic valve in syphilis, however, is characterized by adhesions between the lateral portions of the cusps to the aortic wall of the sinus of Valsalva (Saphir and Scott[23]). Such adhesions produce a narrowing of the sinus, spreading of the commissures, and consequent limitation of the excursions of the cusps. We believe that because of the limited excursions of the cusps the area for settling of bacteria in syphilitic aortitis is much less than in the two previously mentioned conditions and offer this explanation for the rarity of subacute bacterial endocarditis being superimposed on an insufficiency of the aortic valve caused by syphilis.

The outstanding anatomical findings in our 10 cases were subacute bacterial endocarditis, older fibrotic lesions in the heart valves, perivascular areas of fibrosis, and Aschoff bodies in the myocardium. The possibility that the same agent which caused the final subacute bacterial endocarditis might also have caused the Aschoff bodies seems unlikely because the vegetations on the valves were loaded with gram-positive cocci while no organisms could be found within the Aschoff bodies. The question naturally arises as to whether the Aschoff bodies were recent and correspond to the onset of the subacute bacterial endocarditis or whether they were older, possibly dating from the primary rheumatic endocarditis. At first it might appear that the Aschoff bodies in our cases had been present since the first rheumatic infection. If, however, the perivascular areas of fibrosis are regarded as fibrous replacements

of Aschoff bodies, it would be difficult to explain why some of them should maintain their characteristic architecture while others undergo fibrosis. It would seem, therefore, that the Aschoff bodies, in at least some of our heart specimens, were recent and indicate a new rheumatic infection which must have been present at the time of the development of the subacute bacterial endocarditis, the old primary rheumatic infection having healed. It is equally possible that the primary rheumatic myocarditis was chronic and slowly progressive in nature, showing a tendency toward healing (fibrosis) with exacerbations (recent Aschoff bodies) still appearing. From an analysis of the clinical histories of our patients, it cannot be definitely determined whether the symptom-free periods indicate that the previous rheumatic infection had healed and the subsequent rheumatic attacks were new infections, or whether the rheumatic infection was chronic and characterized by periods of quiescence and exacerbations. Although in 2 of our patients the long time-interval between the rheumatic attacks would seem to suggest that the subsequent attack was an entirely new infection rather than an exacerbation of a chronic disease, the repeated attacks at a short time-interval in 5 of the 7 patients with more than one attack cause us to feel that the infection is probably chronic and marked by periods of exacerbations. As suggested by Libman,[24] it may well be that the development of an intercurrent infection, however mild, may serve to reactivate the quiescent rheumatic infection. The fact that in 5 out of 10 patients the clinical picture of rheumatic fever had gradually merged into a characteristic picture of subacute bacterial endocarditis, might be the clinical parallel to the simultaneous presence of Aschoff bodies and subacute bacterial endocarditis. We believe that as the result of an incidental *Streptococcus viridans* bacteremia, bacteria settled upon the primarily diseased valve. This infection, because of the fact that the valve was primarily diseased, possibly also because the older endocardial and myocardial lesions were chronic and progressive in nature, developed in such a fashion as to lead to the picture of a subacute bacterial endocarditis. The finding of Aschoff bodies is significant because they indicate the rheumatic nature of the primary disease.

SUMMARY AND CONCLUSIONS

A clinico-pathological study of 10 cases of subacute bacterial endocarditis, 8 occurring in children and 2 in young adolescents who had been under observation since childhood, is reported. The clinical histories revealed evidence of a preceding rheumatic infection in every instance. Anatomically, all hearts showed healed endocarditis, subacute bacterial endocarditis, and Aschoff bodies in the myocardium, in addition to other changes. The blood specimens revealed pure cultures of *Streptococcus viridans* and smears taken from the vegetations of the heart valves showed gram-positive cocci arranged in chains.

The relation between the rheumatic infection and the final subacute bacterial endocarditis is discussed. A coincidental occurrence of these two conditions, though not definitely excluded, seems unlikely. Although allergy is an attractive explanation of rheumatic fever and its relation to subacute bacterial endocarditis, evidence is brought forward which seems to us to speak against the possibility of rheumatic fever being an allergic phenomenon and also against the assumption that both conditions are manifestations of the same disease, differing only in the immunological response of the host. At the present time the weight of evidence seems to be that the only relationship between rheumatic fever and subacute bacterial endocarditis is that the injury due to a previous rheumatic infection predisposes the valve to a subsequent subacute bacterial endocarditis.

The status of the Aschoff body is discussed and the conclusion reached that the Aschoff body is a characteristic structure and a specific reaction caused by the unknown virus of rheumatic fever. We feel that circumscribed cellular infiltrations produced experimentally in hypersensitive animals, though morphologically resembling, are in no way characteristic of Aschoff bodies. We urge the use of strict criteria for identification of Aschoff bodies.

The fact that in a number of cases the clinical rheumatic manifestations gradually merged into the picture of subacute bacterial endocarditis may account for the presence of recent Aschoff bodies in the myocardium of our patients dying of subacute bacterial endocarditis.

(For discussion see page 107.)

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RHEUMATIC HEART DISEASE

III. Embolic Manifestations*†

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THERE has arisen in recent years a keen interest in the study of the nature of vascular occlusions and in the management of patients with this type of vascular lesion. Considerable investigative work has been done, particularly on coronary thrombosis, thrombophlebitis, and pulmonary embolism. On the continent, especially in Germany, suggestive statistics have been gathered indicating a significant rise in the incidence of vascular thrombosis and embolism during the past two decades. No satisfactory explanation of this occurrence has as yet been found.

It is recognized that in the total incidence of vascular thrombosis and embolism, chronic cardiovascular disease plays a prominent rôle. The significance of arteriosclerosis with lesions of the intima, and of cardiac decompensation with slow blood flow, in the development of coronary, cerebral, and visceral arterial thrombosis, is fairly well established. With regard to embolic manifestations, however, the problem is more obscure. A search of the literature reveals that previous studies have centered mainly on the problems of postoperative and postpartum pulmonary embolism. Information as to the relative rôles of various types of heart disease in the incidence of embolic manifestations is not available; and although clinical experience suggests that among patients with "medical" diseases who develop embolism, rheumatic heart disease is frequently present, no reports exist, so far as we know, dealing with this problem statistically. This presentation aims, therefore, to shed some light on the rôle and the clinical nature of embolic manifestations in patients with rheumatic heart disease. The problem contains several practical as well as theoretical aspects.

The basis of the present investigation is a combined analysis of the clinical and the post-mortem data of 5,215 consecutive autopsies performed in the Boston City Hospital during a twenty-five-year period, ending with 1929. Such a combined consideration of clinical and laboratory findings, with the morphological changes observed post mortem, is essential in establishing the relationship between the occurrence of rheumatic heart disease and the *degree* of disability as seen in the

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clinic. Thus, although the total number of cases of rheumatic endocarditis was as high as 474, an incidence of 9.1 per cent, in only 164 instances was the cardiac damage directly responsible for death.[1, 2] These 164 cases, representing on the whole the most advanced type of rheumatic cardiac damage, were then analyzed as to the presence or absence of embolism and thrombosis. Obviously a differentiation between thrombosis and embolism, even when post-mortem examination is available, cannot always be made with certainty. The clinical manifestations of the onset, the presence or absence of endocardial thrombi, and the character of the occluding plug often, but not always, help in this differentiation.

FREQUENCY AND DISTRIBUTION OF INFARCTIONS

As the absolute differentiation of vascular embolism and thrombosis is not always possible, although in the majority of instances the combined clinical and post-mortem data indicated embolus as the cause of infarct, we shall present embolic manifestations as infarcts. Visceral or pulmonary infarction, single or multiple, involving one or more organs was found in 73 patients (45 per cent). In 1 additional patient thrombosois of the femoral vein was present, and in 11 additional patients extensive ante-mortem auricular thrombi were present without embolic manifestations. This estimation of infarction during the course of rheumatic heart disease must be considered conservative for the following reasons: (1) Emboli may have occurred in the past without leading to infarct or the infarct may have completely healed; (2) some emboli in the skin and in the extremities, which organs were not examined with sufficient thoroughness post mortem, were in all probability overlooked; and (3) owing to the fact that permission to examine the brain was not always obtained, cerebral embolism may have been overlooked in some instances.

TABLE I

DISTRIBUTION OF SITES OF INFARCTION

Patients With Infarcts in One Organ

	NO. OF CASES
Lungs	16
Brain	9
Kidneys	7
Spleen	5
Arteries of legs	2
Mesenteric artery	1
Aorta and iliac arteries	1
Total No. of Cases	41

Single or multiple infarction of one organ was present in 41 patients (Table I); in 22 instances single or multiple infarcts involved two organs (Table II); and in 10 patients infarcts were present in three or

more organs (Table III). The organs involved, in the order of frequency, were: lungs 31, brain 28, kidneys 25, spleen 18, extremities (aortic, iliac, and femoral arteries) 10, intestines (mesenteric artery) 5, and liver 1.

In 4 of the 16 patients with infarcts confined to the lungs, mural thrombi of the right auricle were the source of the embolus, and in two instances venous thrombosis was the source. One patient showed a large thrombus in a branch of the pulmonary artery. Thus the source of the embolus could be explained in only 6 of the 16 cases. In the

TABLE II

DISTRIBUTION OF SITES OF INFARCTION

Patients With Infarcts in Two Organs

	NO. OF CASES
Lungs and spleen	4
Lungs and kidneys	4
Brain and lungs	3
Brain and kidneys	3
Brain and spleen	2
Kidneys and spleen	2
Kidneys and iliac arteries	1
Lungs and femoral artery	1
Brain and liver	1
Brain and mesenteric artery	1
Total No. of Cases	22

TABLE III

DISTRIBUTION OF SITES OF INFARCTION

Patients With Infarcts in Three or More Organs

	NO. OF CASES
Brain, kidneys, and spleen	3
Brain, mesenteric artery, and arteries of leg	1
Brain, lungs, and spleen	1
Brain, kidneys, and aorta	1
Brain, kidneys, and iliac artery	1
Brain, lungs, kidneys, and intestines	1
Brain, lungs, kidneys, and arteries of leg	1
Kidneys, spleen, mesenteric, iliac, and femoral arteries	1
Total No. of Cases	10

group of 15 patients with combined lung and organ infarcts a source of the embolus was revealed in 9. Thus, in 6 of this latter group and in 10 of the former group, or in approximately half of the cases, no obvious source of emboli has been found. In 5 instances of the unexplained group of 16, however, there was an acute vegetative process over the tricuspid valve. Pulmonary infarction is sometimes attributed to local thrombosis of the pulmonary vessels as a result of slow pulmonary circulation. This condition instead of embolism may well have been a factor in these cases. The finding of plausible embolic sources of the infarcts in about 50 per cent of the cases, however, places the

burden of proof on those who maintain that in these instances the infarcts were caused by local circulatory factors.

Cerebral infarction was the cause of death in 22 cases of the present series, and in one additional case it was regarded as a contributing cause of death. In the 10 cases in which post-mortem examination of the brain was made, cerebromalacia or cysts were found. The cerebral lesions were localized in the internal capsule, the basal ganglia, the restiform body, and the occipital lobe. In every patient with cerebral lesions clinical symptoms were present, and experience with cases not included in this series indicates that the occurrence of cerebral embolism with symptoms and with complete functional recovery and absence of demonstrated infarction is not uncommon. The regularity of clinical manifestation in cerebral embolism is in sharp contrast to the frequent lack of clinical recognition of infarcts of the spleen, kidneys, and other organs.

THE RÔLE OF THE EMBOLIC FACTOR IN THE CAUSATION OF DEATH

The estimation of the rôle of embolism or infarction in the causation of death was often difficult because of the simultaneous presence of other bodily derangements. For this reason the embolic manifestation was held responsible for death only when the clinical condition of the patient took a sharply defined downhill course following the vascular accident.

It is well appreciated that complete recovery, or partial clinical recovery with life of years' duration, following an embolus is not a rare occurrence. Thus, in the present series the combined clinical and post-mortem studies indicated that in at least 11 patients infarcts occurred at some time in the past course of the illness. In 1 patient, a man fifty-five years of age, complete hemiplegia due to embolism developed as long as fourteen years before his last entrance into the hospital. In another case, a female patient thirty-five years of age, embolism in the right femoral artery necessitating amputation of that leg developed while she was in the hospital three and a half years before the fatal cerebral embolism.

TABLE IV

RÔLE OF EMBOLISM IN 164 DEATHS FROM RHEUMATIC HEART DISEASE

	NO. OF CASES	PER CENT
Causing death	26	16
Contributing to death	8	5
Probably contributing to death	10	6
Not contributing to death	29	18

Table IV presents a conservative estimate of the frequency of death due to embolism in the 164 cases of fatal rheumatic heart disease. Accordingly in 26 instances, or 16 per cent, death was caused by embolism;

in an additional 8 cases, or 5 per cent, the embolic accident definitely contributed to the occurrence of death. In 10 cases, or 6 per cent, there was suggestive but not conclusive evidence of the contributory influence of embolism. In 17 of the 26 instances of fatal embolism, the accident occurred in patients with slight or no evidence of circulatory failure up to the time of infarction; in the remaining 9 patients there existed a considerable degree of circulatory insufficiency. In this series of 164 cases, as well as in other instances, following the occurrence of embolism, particularly in the brain, lungs, and extremities, the existing circulatory impairment often became intensified, and at times circulatory insufficiency developed in patients with hitherto efficient circulation.

The brain was by far the most frequent site of fatal emboli. In only one instance was embolism of a large branch of the pulmonary artery definitely the cause of death. In 11 other instances pulmonary infarction played an important contributing part, and in 7 cases it played a suggestive rôle. The relation of the pulmonary infarcts to pneumonic processes was often not sufficiently clear to indicate the rôle of the infarcts in the pathogenesis of the pneumonia. Our analysis indicates that in 34 cases of fatal rheumatic heart disease, or 21 per cent, embolism played a chief or contributing part in the death of the patient.

AURICULAR FIBRILLATION AND EMBOLIC MANIFESTATIONS

The cardiac rhythm was determined in 131 of the series of 164 cases. Persistent or paroxysmal auricular fibrillation or flutter was present in 74 patients, or 57 per cent. In a group of 28 patients with extensive auricular thrombi the rhythm was determined in 25, and of this number 22, or 88 per cent, exhibited auricular fibrillation. This high incidence of fibrillation suggests a relationship between auricular fibrillation and the formation of mural thrombi. This is not unexpected, in view of the dilated left auricle which fails to contract.

THE RELATION OF MURAL THROMBI TO THE STATE OF RHEUMATIC ACTIVITY

Auricular endocarditis in addition to valvular endocarditis occurred in a large number of cases in the series. The question was therefore raised as to whether active carditis plays a rôle in the formation of mural thrombi. Rheumatic activity of the heart was determined by the presence alone or in combination of recent rheumatic arthritis, chorea, acute valvulitis, the presence of Aschoff bodies, and the presence of acute pericarditis not otherwise explained. The combined clinical and post-mortem study revealed an activity during the last admission or post mortem in 70 cases, or 43 per cent; recent activity in 7; and suggestive evidence of activity in 13. In 74 patients activity was not

present. Among the 28 patients with auricular thrombi, activity was definitely present in 5; in 1 patient there was suggestive evidence of activity. Thus activity was present in but 18 per cent as contrasted with 47 per cent of the entire series. Activity is therefore not a factor of primary importance in the formation of mural auricular thrombi in the course of rheumatic heart disease.

SOURCES OF EMBOLI

Definite sources of emboli were found in only 30 of the 73 patients with infarcts. This number includes only those instances of mural thrombi which exhibited definite organization and firm attachment to the wall. In 7 patients with vegetative processes over the valves, the thrombus was prominent. There were a number of instances in which small verrucous vegetations were present over the valves, but the evidence that these vegetations were the source of emboli was insufficient. As the clinical history in the patients without determined source of emboli frequently indicated embolism rather than thrombosis, the explanation of the failure to find the source of the emboli must lie in one of two possibilities: (1) Either the local cardiac thrombi corresponded to the infarct and the source was completely dislodged; or (2) the small verrucous vegetation observed may have been the cause of embolic manifestations.

CLINICAL CONSIDERATIONS

It is evident from the data presented that embolic episodes and infarction occur frequently during the course of rheumatic heart disease, and that these accidents represent a significant rôle in the incidence of death. As observations of patients indicate that purpuric skin lesions or petechiae may also occur in rheumatic heart disease, it follows that embolic manifestations and purpuric spots alone or in combination do not necessarily indicate subacute or acute bacterial endocarditis. Statistically the association of these manifestations with regular cardiac rhythm favors the diagnosis of subacute or acute bacterial endocarditis, and their association with auricular fibrillation the diagnosis of rheumatic endocarditis.

In order to estimate the comparative frequency of peripheral arterial embolic manifestations due to rheumatic heart disease and of embolism caused by other diseases, the underlying etiology of 48 consecutive cases of cerebral embolism occurring in medical wards was determined. The diagnosis was considered definite clinically in every case of the group. Cerebral embolism has been chosen for comparison because, as was shown above, embolism of the brain regularly produces clinical syndrome. In this group of 48 cases, rheumatic heart disease was considered as the source of embolism in 23 instances, chronic myocardial degeneration caused by arterial hypertension or arteriosclerosis in 11 instances, sub-

acute bacterial endocarditis in 9, auricular fibrillation of undetermined etiology in 2, and other causes in 3 instances. Thus, rheumatic heart disease was responsible for the occurrence of embolism more often than any of the other diseases.

There are a few additional bedside observations to which we should like to call attention. 1. It is stated that in visceral embolism the onset of symptoms, and particularly of pain, is sudden. A careful analysis of the patient's sensation reveals, on the other hand, that in splenic and kidney infarcts particularly, the pain often starts as a mild discomfort which slowly or rapidly, in the course of minutes or hours, increases to severe pain. In view of the fact that these organs themselves are not sensitive to pain, but it is their capsule or peritoneal covering which induces pain reflexly, it seems probable to us that in the origin of pain secondary fibrinous perivisceritis plays the important rôle.

2. Because emboli lodged in the larger vessels, particularly in the lower portion of the aorta and the subclavian, radial, brachial, iliac, femoral, popliteal, tibial arteries, can be removed with relative ease and safety provided the diagnosis is made promptly, knowledge of the variations in the clinical picture of embolism along the vessels is important. In addition to the recognition of embolic manifestations of the extremities with classic clinical picture, it is important to appreciate that embolism is not always associated with excruciating pain over the extremities, but coldness, tingling, or numbness may be the only subjective sensation. These mild complaints in patients with heart disease, and particularly with auricular fibrillation, should lead us to careful examination.

3. The result of surgical removal of emboli, as is known, is good if the diagnosis is made within five hours of onset, and fair up to fifteen hours. At times no reliable history exists as to the onset. In 3 cases in which the onset of embolism could not be determined, the patients exhibited marked tenderness on pressure along the arteries below the site of the embolus, and exploration revealed a secondary arterial thrombosis with hemorrhagic inflammatory reaction of the adventitia of the arteries. In these cases surgical interference was of no help. This sign, if confirmed on a larger number of cases, may be a guide in determining contraindication against surgical interference.

Embolism of the arteries of the extremities does not always result in gangrene, and hence in some instances conservative management through establishment of efficient collateral circulation is followed by complete or partial recovery. The decision between conservative care and embolectomy is a difficult and a delicate one. Partial occlusion of the artery, mild symptoms and signs of ischemia below the site of occlusion, good cardiac function, an elapse of a relatively long period after the onset, and occluded artery with good supply of collateral branches favor,

on the whole, conservative management. Any evidence of greatly inadequate blood supply below the site of occlusion calls for prompt surgical interference.

SUMMARY

1. Infarction of one or more organs occurred in 73 cases, an incidence of 45 per cent, of a group of 164 cases in which death was caused by rheumatic heart disease. In 41 instances one organ, in 22 instances two organs, and in 10 instances three or more organs were involved by single or multiple infarcts. The organs involved in order of frequency were: lungs 31, brain 28, kidneys 25, spleen 18, extremities 10, intestines 5, and liver 1.

2. A conservative estimate revealed that in 34 cases, or 21 per cent of the total group, embolism played a chief or contributing part in the death of the patients. Embolism plays, therefore, a significant rôle in the causation of death in rheumatic heart disease.

3. A statistical consideration suggests that auricular fibrillation rather than active rheumatic endocarditis of the auricles plays the primary etiological rôle in the formation of auricular thrombi.

4. Rheumatic heart disease, more than any other type of heart disease, is responsible for embolic manifestations.

5. Clinical considerations bearing on embolic manifestations are discussed.

(*For discussion see p.* 114.)

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MITRAL STENOSIS*

A Clinical and Pathological Study of One Hundred Cases*

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ALTHOUGH correlation of clinical data and pathological findings in cases of mitral stenosis has been repeatedly done[1, 2, 3, 4, 5] in the light of present-day concepts of heart disease, it is important to reexamine the facts. The anatomical features were studied by Morgagni in 1762, but the clinical features were not adequately recognized until the reports of Bouillaud in 1835,[6] and it is to him that we are indebted for much of the modern clinical knowledge of this valve lesion. Bouillaud emphasized the frequency of the association of endocarditis and pericarditis with myocarditis. He said: "I have never met a case of carditis [myocarditis as we know it] which was not complicated with endocarditis or pericarditis, and I must admit that the symptoms of these last two inflammatory conditions took my entire attention." Bouillaud also observed the relation of endocarditis to the valvular lesion and its recurrence in cases in which such lesions have once developed.

During the period 1920-1933 100 cases of advanced mitral stenosis came to autopsy at the Cleveland City Hospital, the majority of which had been seen clinically by one of us. The cases of mitral stenosis in a total of six thousand autopsies were distributed evenly over these years. By advanced mitral stenosis we imply the typical fish-mouth or buttonhole deformity of the valve, and we have not included cases showing slight or early pathological evidence of mitral stenosis. These 100 autopsied cases, 70 of which were reviewed in 1931,[7] form the basis of this report.

CLINICAL FEATURES

Rheumatic Fever.—Of the 90 cases in which a careful history could be obtained there was a history of multiple migratory arthritis in 51 cases (56.6 per cent). Thirty-four patients (66.6 per cent) had but one attack; 13 patients (25.3 per cent) had two attacks; 3 patients (6 per cent) had three attacks; and 1 patient had four attacks. Seven patients (7.7 per cent) gave a history of chorea. A history of scarlet fever was obtained in 3 cases; frequent sore throats were recorded in 10 cases.

*From the Medical Clinic of Western Reserve University at City Hospital.
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Fever.—A temperature above 38° C. was recorded many times during the fatal illness of these patients, and an effort was made to correlate this clinical finding with active cardiac infection. No conclusion could be drawn, as fever was frequently present without pathological evidence of active infection in the heart.

Cerebral Accidents occurred in 12 instances. In 2 of these patients subacute bacterial endocarditis was present; in one patient there was a *Staphylococcus albus* septicemia and a frontal lobe abscess with acute vegetations on the mitral and aortic valves. In one patient (aged thirty-six years) there was a basilar hemorrhage without evidence of arteriosclerosis (or hypertension) or syphilis. In 2 patients there was a history of hemiplegia four years and eight years, respectively, prior to admission to the hospital. In one patient there was a history of hemiplegia on three occasions prior to the last admission (with residual left sided paresis). One patient gave a history of facial paralysis, but the brain was not examined post mortem and the nature of the lesion could not be determined.

Sex and Age.—There were 53 males and 47 females, although the ratio of male to female patients on the medical service was as 3:2, substantiating previous reports concerning the higher percentage of mitral stenosis in females. The sex and age distributions are illustrated in Fig. 1-A and B, in which all of the cases are tabulated. In Fig. 1-A are tabulated the male cases while in Fig. 1-B are tabulated the female cases. The age distribution is much the same in the two graphs, although the male patients past fifty years of age outnumbered the female patients (M 16, F 7). The average age of death of all of the patients was forty and six-tenths years; the average age of the males was forty-two and seven-tenths years, and the average age of the females was thirty-eight and six-tenths years. These figures agree with those reported by previous writers.

Race.—There were 9 negro patients: 3 males and 6 females. This total percentage of 9 per cent may be compared with the negro population of the medical service of City Hospital which is 20-30 per cent of the total. Davis and Weiss report 3.8 per cent negroes in their 474 rheumatic heart deaths as compared to 8 per cent negroes of the total autopsy series. Whether this apparent lower percentage of rheumatic heart disease in colored patients is due to migration (as suggested by Davis and Weiss) or whether the incidence is actually lower cannot be determined definitely.

In studying Fig. 1, 72 patients or 72 per cent died between the ages of twenty and fifty, the largest number dying in the fourth decade (32 per cent). The sexes shared nearly equally in the mortality between the ages of twenty and fifty. It is seen that in the majority of our cases death occurred before the age of fifty. The 5 cases of

subacute bacterial endocarditis are seen in the diagram as solid black blocks and all occurred before the age of fifty years. The series of Davis and Weiss[8, 9] comprising 474 autopsied cases of rheumatic heart disease showed that 164 cases (34.5 per cent) of the total group died directly as the result of rheumatic heart disease, whereas in our 100 cases of mitral stenosis 81 or 81 per cent died directly as the result of rheumatic heart disease (heart failure). If the case of acute and the 5 cases of subacute bacterial endocarditis are included, this figure

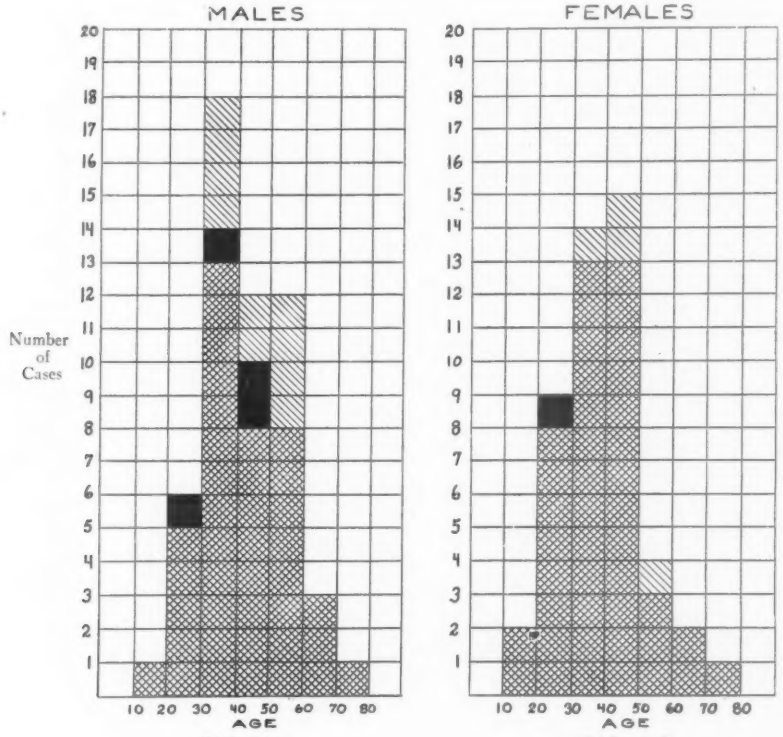

FIG. 1 A FIG. 1 B

rises to 87. When the noncardiac deaths are subtracted from the series (the lighter areas at the top of the columns of Fig 1, A and B), it is seen that the predominance of deaths up to the age of fifty is still present.

Effect of Pregnancy on the Length of Life.—Recent clinical studies have lessened the fears of clinicians in dealing with pregnancy in mitral stenosis.[10, 11, 12, 13] Our cases emphasize the small part pregnancy plays in bringing on failure or as a cause of death. In the 47 female patients in this series there were 5 who were unmarried. In 10 cases there were no children and in 7 cases our history was uncertain. The remaining women (25) bore children as seen in Table I.

The average age of these 25 women who bore children was thirty-nine and four-tenths years. The average age of the women who did not bear children was forty-one years (excluding from this figure two children aged thirteen years and fourteen years). The average age

TABLE I

NO. OF CHILDREN	NO. OF PATIENTS
1	8
2	6
3	2
4	1
5	0
6	2
7	4
8	1
9	0
10	0
11	0
12	0
13	1

of all the females was thirty-eight and six-tenths years and the average age of all the males was forty-two and seven-tenths years. These figures suggest that the life span is only slightly reduced in women who bear children. A careful study of our cases reveals a number of instances in which there may have been some influence exerted by pregnancy.

CASE 9.—One child (cesarean) two years before death; died of bronchopneumonia.

CASE 21.—Died two weeks after delivery (failure). First pregnancy.

CASE 42.—Abortion at sixth month of pregnancy.

CASE 52.—Had failure after childbirth, fourteen months before death. Second child.

CASE 63.—Heart trouble at fourteen; six children and four miscarriages. Died at age of forty years of streptococcus septicemia following induced abortion.

CASE 95.—Died two weeks after birth of second child; had failure all through pregnancy.

The following case emphasizes the fact that multiple pregnancies may not apparently affect the life span of the patient.

CASE 13.—Had thirteen children, last one born at age of forty-one; failure at forty-three, died at forty-eight.

There appears to be a definitely deleterious effect of pregnancy in women with mitral stenosis when failure or marked reduction in exercise tolerance antedates pregnancy. That the great majority of rheumatic hearts bear pregnancy well seems evident. This view is shared by Daly,[10] Reid,[11] and Hamilton and Kellogg.[12]

Auricular Fibrillation.—In 94 cases the mechanism was accurately, and in most instances electrocardiographically, studied. Auricular fibrillation was present in 50 cases or 53.1 per cent. Normal mechanism was present in 43 cases and heart-block in one case. In 52 cases

pulmonary infarcts were found post mortem of which 46 cases were carefully studied as to mechanism. Thirty of these or 65 per cent had auricular fibrillation. Intracardiac thrombi were frequently associated with auricular fibrillation (22 out of 37 cases). In none of the 5 cases of subacute bacterial endocarditis did auricular fibrillation occur.

The rarity of auricular fibrillation in subacute bacterial endocarditis has been noted by Levine and Fulton.[14] Likewise, Rothschild, Sacks, and Libman[15] observed that auricular fibrillation was unusual in subacute bacterial endocarditis, finding but one case in 109 patients in the active or bacterial phase of the disease, and in 3 patients among 14 cases in the bacteria-free or healed stage. The rarity of auricular fibrillation in subacute bacterial endocarditis[15] may be explained in part by the rarity of subacute bacterial endocarditis in advanced mitral stenosis. Auricular fibrillation is definitely more common in mitral stenosis, especially in advanced cases.

Blood Pressure.—Boas and Fineberg[16] and Levine and Fulton[17] have recently reemphasized the relationship between mitral stenosis and hypertension. In 7 cases hypertension was observed, but in view of the late stage of many of our hospital admissions this figure is doubtless too low to be compared with the clinical observations of the other investigators.

Incidence of Tuberculosis.—Rokitansky,[18] in 1846, wrote that heart disease accompanied by chronic passive congestion of the lungs excluded pulmonary tuberculosis. Tileston,[19] in 1908, reviewed the conflicting literature and reported a series of 128 autopsied cases of mitral stenosis which showed a much lower percentage of pulmonary tuberculosis than the material from which they were drawn. The greater the stenosis the less was the incidence of tuberculosis and the patients with a high degree of stenosis were free from active tuberculosis. Tileston believed that pulmonary tuberculosis is less likely to occur in mitral stenosis, and if present runs a milder course and tends to heal. This he believed was due to the chronic pulmonary congestion. Three of our patients had chronic fibroid tuberculosis and one additional patient had tuberculous mesenteric lymph nodes.

Causes for Hospitalization and Duration of Failure.—Eighty-one cases or 81 per cent were admitted to the hospital because of congestive failure of varying degree. The duration of the failure from the onset of symptoms to death varied greatly and averaged three and a half years.

Subacute Bacterial Endocarditis.—The importance of this superimposed infection as a cause of death from heart disease may be judged from the figures of Davis and Weiss[9] who reported finding 47 cases of subacute bacterial endocarditis in a total of 474 necropsies

of rheumatic heart disease (9.9 per cent). In the 269 cases in which death was attributable to cardiac disease this number, 47, represents a percentage of 17.4 per cent. Subacute bacterial endocarditis occurred in 5 cases of our series. In 88 cases of our series death could be directly attributable to heart disease either due to infection or to failure. In this group there were 5 cases of subacute bacterial endocarditis (5.6 per cent). During the period covered by our studies there were 40 autopsied cases of subacute bacterial endocarditis, so the percentage of mitral stenosis in this small series was 12.5 per cent. These facts substantiate the findings of Fulton and Levine[17] and of Sprague.[20] The latter author found mitral stenosis 5 times in a series of 20 cases of subacute bacterial endocarditis (25 per cent) which were not autopsied. The calcified and comparatively avascular scar may be responsible for this infrequency. The immobility of the mitral valve in advanced stenosis and the consequent absence of trauma to the valve during systole has also been suggested as a cause of the infrequent association of these two conditions. Of interest was the finding of combined rheumatic valve lesions in all 5 of our subacute cases and in all but one the mitral valve was seriously involved with the superimposed infection. In this one case with slight rheumatic scarring of the aortic valve, the lesions were almost exclusively limited to this valve.

Acute Bacterial Endocarditis likewise was uncommon and occurred in only two instances. One patient had septicemia due to *Staphylococcus albus* and died of a cerebral hemorrhage (male, white, aged thirty-three years). Another patient had septicemia following an abortion. There were 13 cases of acute bacterial endocarditis autopsied during the period covered by these observations, the majority of which were due to pneumococcus endocarditis in pneumonia.

Causes of Death.—Eighty-one patients or 81 per cent died directly as the result of cardiac disability attributable to the rheumatic heart disease. In addition, 5 or 5 per cent died of subacute bacterial endocarditis. Besides congestive failure and acute and subacute bacterial endocarditis, there were indirect causes of death as the result of heart disease, the cases with embolism and with infarction with varying degrees of failure.

Heart Weights.—Table III shows the heart weights in summary. Examination of Table III reveals a great variation in the heart weights, although the average weight of the hearts with combined lesions tends to be greater. The wide range of weights makes it difficult to draw any conclusions concerning the influence of the associated valve lesions.

TABLE II

SUMMARY OF PATHOLOGICAL FINDINGS

THE PATHOLOGICAL FINDINGS IN THE CARDIAC DEATHS		
Failure alone		68 or 68%
Failure associated with:		13 or 13%
Coronary sclerosis and occlusion	1%	
Bronchopneumonia	5%	
Pulmonary embolism	1%	
Large pulmonary infaret	1%	
Cerebral hemorrhage	1%	
Erysipelas	1%	
Acute salpingitis	1%	
Uremia and hydronephrosis due to carcinoma of cervix	1%	
Encephalomalacia	1%	

PATIENTS DYING OF PRIMARY CAUSES OTHER THAN CARDIAC FAILURE	
Subacute bacterial endocarditis—with no failure	3
with slight failure	2
Encephalomalacia and bronchopneumonia	2
Acute bacterial endocarditis and cerebral hemorrhage *(Staphylococcus albus)*	1
Arteriolar disease with hypertension with bronchopneumonia and heart-block	1
Carcinoma head of pancreas and encephalomalacia	1
Erysipelas with septicemia *(Streptococcus hemolyticus)*	1
Bronchopenumonia and pyonephrosis	1
Bronchopneumonia	2
Lobar pneumonia	1
Carcinoma of stomach	1
Pernicious anemia with bronchopneumonia	1
Septicemia following abortion	1
Purpura hemorrhagica	1

Tricuspid Valvulitis (varying degrees of stenosis).—When mitral stenosis was associated with aortic stenosis, the tricuspid valve was involved in 12 per cent of the cases, while mitral stenosis was associated with tricuspid stenosis alone in only 5 per cent of our series. This is in agreement with the published series of Dressler and Fischer[21] who found mitral, aortic, and tricuspid stenosis present in 11 instances in a series of 120 cases of valvular heart disease (9.1 per cent).

Associated Valve Lesions (without stenosis).—The aortic valve was scarred in 20 per cent; the tricuspid valve in 15 per cent, and the pulmonic valve in 2 per cent.

TABLE III

	%	AVERAGE WT. IN GM.	RANGE OF WT. IN GM.
Mitral stenosis alone	54	462.7	250–700
Mitral stenosis with aortic stenosis	29	530.0	250–925
Mitral stenosis with aortic and tricuspid stenosis	12	545.8	300–750
Mitral stenosis with tricuspid stenosis	5	470.0	425–525

Pericarditis.—Chronic adhesive pericarditis was found in 10 per cent of the cases and acute pericarditis in 1 per cent.

Acute Verrucose Endocarditis.—In substantiating the original findings of Bouillaud, we observed acute verrucose endocarditis in 48 per cent of our cases. This agrees with the clinical observations of Cutler, Levine and Beck.[22] Acute vegetations were found on the mitral valve in 42 per cent; on the aortic in 29 per cent; on the tricuspid in 9 per cent; and on the pulmonic valve in 2 per cent.

Intracardiac Thrombi were found in 37 cases as seen in Table IV. Thrombi and infarction were more common in the presence of acute verrucose endocarditis.

TABLE IV

Right ventricle	4	10.8% of 37 cases
Left ventricle	2	5.4% of 37 cases
Right auricle	16	43.2% of 37 cases
Left auricle	19	51.3% of 37 cases

The cardiac mechanism was studied in these 37 cases, in 34 of which the data were reliable. Table V is a tabulation of the findings.

TABLE V

Auricular fibrillation	22	64.7%
Normal sinus rhythm	12	35.3%
No record	3	8.1%

Infarction of various viscera was present in 52 cases and the distribution is seen in Table VI, together with cardiac mechanism.

TABLE VI

		MECHANISM		PER CENT
Pulmonary	33	Auricular fibrillation	30	65.2
Renal	21	Normal sinus rhythm	16	34.9
Splenic	13	Not recorded	6	11.5
Hepatic	1			

No definite relationship could be established between the presence of intracardiac thrombi and visceral infarction.

The incidence of auricular fibrillation in the entire series was 53.1 per cent, in the cases having intracardiac thrombi 64.7 per cent, and in 65.2 per cent of the cases showing infarction of various organs. A definite relationship can be made out between the occurrence of auricular fibrillation and the finding of intracardiac thrombi and of infarction.

Pulmonary Embolism was present in 7 cases. Thrombi were found in various other vessels:

Coronary arteries	2
Subclavian arteries	2
Optic artery	2
Common iliac artery	1
Abdominal aorta	1
Renal artery	1
Portal vein	1

Cholelithiasis.—Brockbank[23] found cholelithiasis in 21.8 per cent of 87 cases of mitral stenosis, while in 1347 post mortems gallstones were present in 7.4 per cent. Gallstones were present in 3 per cent of our cases. There appears to be no relationship between chronic cardiac failure as caused by mitral stenosis and the formation of gallstones.

SUMMARY

In a clinical pathological review of 100 autopsied cases of advanced mitral stenosis the findings of previous investigators have largely been substantiated.

1. A rheumatic history was obtained in 56.6 per cent, and 66.6 per cent of these cases had but one attack.

2. Cerebral accidents occurred in 12 instances.

3. Females and the white race predominated. The average age of death of the males was forty-two and seven-tenths years; of the females thirty-eight and six-tenths years. Pregnancy did not appear to influence greatly the onset of failure, nor did it directly cause death.

4. Auricular fibrillation was present in 53 per cent; intracardiac thrombi and pulmonary infarction were in the majority of the cases associated with auricular fibrillation. In none of the 5 cases of subacute bacterial endocarditis was fibrillation present.

5. Chronic fibroid tuberculosis was found in 3 cases.

6. Eighty-seven patients died as the result of cardiac disability. Eighty-one per cent of the patients died of circulatory failure, and subacute bacterial endocarditis was an uncommon cause of death (5 per cent). Acute bacterial endocarditis occurred once. Acute verrucose endocarditis was present in 48 per cent of the cases.

7. Mitral stenosis was the sole lesion in 54 per cent of the cases. Tricuspid stenosis was more frequently associated in the patients having aortic stenosis.

8. The heart weight tends to increase with multiple valve lesions.

9. Auricular fibrillation was more frequent in the cases with intracardiac thrombi and with infarction of various origins than in the entire series.

10. Cholelithiasis was present in only 3 per cent of the series.

(*For discussion see p.* 113.)

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RHEUMATIC HEART DISEASE IN SOUTHERN FLORIDA*

Incidence and Clinical Notes

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THIS paper represents an attempt to present a picture of rheumatic heart disease as it occurs in Southern Florida (Miami), together with a review of the literature bearing on the geographical distribution of rheumatic heart disease. The incidence of the disease has been determined by examination of hospital records, private case records, and through a survey of school children. Although the groups are relatively small, it is hoped that the value of the data is enhanced by the strictly personal nature of the inquiry.

INCIDENCE OF RHEUMATIC FEVER

A previous survey[1] of patients admitted to Jackson Memorial Hospital, Miami, during the years 1925 to 1930 revealed only 4 cases of rheumatic fever and 6 cases of chorea among 31,153 admissions. From 1930 to 1933 there have been only 4 additional cases of rheumatic fever and none of chorea among 16,286 admissions, making a total of 14 cases of rheumatic fever or chorea among 47,439 total admissions. Approximately 13,000 were medical cases, giving an incidence of practically 1 case of rheumatic fever or chorea per thousand medical cases. The hospital admits patients from all walks of life with a number of children included. About one-fifth of the medical admissions were colored patients, but only one instance of rheumatic fever occurred in this race. The ages of the 4 cases since the previous report ranged from eleven to twenty-four years. The cases were mild, monocyclic in type, with carditis apparent in one only, a woman twenty-four years of age who is the only adult Miamian I have ever known to develop an initial attack of rheumatic fever.

Among approximately 4,200 private patients seen in the office and home by the author during the same eight-year period (1925 to 1933) there have been only 3 cases of rheumatic fever or chorea originating in Miami, and one of these is included in the foregoing hospital group. By combining the two groups a total of 16 cases of rheumatic fever or chorea were encountered among 16,200 medical cases.

Because of some supposed relationship between scarlet fever and rheumatic fever, it should be noted that scarlet fever occurred four times more frequently than rheumatic fever, there being a total of 65 cases during the eight-year period, in the combined series. On the other

*Read before the American Heart Association, Milwaukee, Wisconsin, June 13, 1933.

hand, acute nephritis is just as rare in this area as is rheumatic fever, there being 15 cases in the hospital series and none seen in private work.

RHEUMATIC HEART DISEASE

During the years 1931 and 1932 there were 224 patients with heart disease admitted to the wards of Jackson Memorial Hospital under my supervision. Rheumatic heart disease was the etiological diagnosis in 57 cases, or 25.9 per cent. It might seem that since this figure is not much smaller than that of similar morbidity statistics from northern hospitals that Miami clinicians must be overlooking the rheumatic type of heart disease in its inception, if the incidence of clinical rheumatic fever is so low. But further analysis shows that in the rheumatic group of 57 patients only 2 or 3.3 per cent were natives of southern Florida while 22 or 10 per cent of the entire group claimed the Miami area as their birthplace. In the rheumatic group there were 9 negroes (14 per cent), but there were 64 or 28.5 per cent in the entire group. The ratio of rheumatic heart disease among the 160 white patients was more than double that in the colored, being 30 per cent or 48 cases.

During the same period in a small cardiac clinic conducted by the author, 47 patients with organic heart disease were cared for, and of these 14 or 29.9 per cent had rheumatic heart disease, but only 3 of the rheumatic patients were born in the Miami area.

Among 142 patients with organic heart disease under observation in private work during the past two years, there were 32 or 22.5 per cent with rheumatic heart disease. Only one of this type was a native of southern Florida however, while 10 per cent of the entire group were born in this area.

Combining the three groups of hospital, clinic, and private cases, gives a total of 413 patients with organic heart disease studied during the two-year period, with rheumatism the etiological factor in 103 or 24.9 per cent. Only 6 patients with rheumatic heart disease were natives of southern Florida.

During the same period 42 instances of heart disease were found at autopsy, with 7 hearts showing morphological evidence of rheumatic etiology, giving an incidence of 21.4 per cent. None of the 7 patients had been natives of southern Florida.

School Survey.—Because of the likelihood of mild attacks of rheumatic fever in children being overlooked, thus making the disease appear rarer than it actually is, an examination of elementary school children (Grades I to VI) in the Miami area was made. Fifteen hundred children born in Miami (including children coming to Miami during the first year of life in some cases) and a similar group of children born in northern states were examined by the author in the past year.* (For

*The following physicians kindly cooperated in the examination of some of the school children: Dr. Wm. McKibben, Dr. Donald Gowe, Dr. Dan Hardie, and Dr. Rothwell Lefholz.

practical purposes any child born north of Florida was included in the northern group, but the majority of these children had moved to Miami from above the Mason and Dixon line.) A record was made of all cases of heart disease found during the examinations. In a few instances x-ray and electrocardiographic examinations were used as an aid in establishing the diagnosis in questionable cases, but for the most part reliance was placed on the accepted physical signs of heart disease in children. Undoubtedly some mistakes were made, but since all questionable cases were seen by the same examiner (the author), it is likely that the rate of incidence in the two groups is fairly accurate.

Among the children born in the Miami area there were 7 cases of rheumatic heart disease, only one of which showed marked signs of mitral stenosis. A history of rheumatic fever was obtained in 2 cases only. In the northern group 24 children showed signs of rheumatic heart disease, but 2 of these gave a history of having their first attack of rheumatic fever after moving to Florida. Even making allowance for such an event in other cases, this survey indicates that rheumatic heart disease is found in children born in the Miami area about one-third as frequently as in children who have moved to southern Florida from the North. But in view of the extremely low incidence of clinical rheumatic fever in the Miami area, it is surprising to find even 7 cases (an incidence of 0.46 per cent) of rheumatic heart disease among Miami born children. Very likely the insidious invasion of the heart is undetected in its active state by parents and physicians alike.

In passing it should be noted that among the 3,000 children there were 84 instances of systolic murmur classified as functional, about equally divided between the two groups. Of course some of these murmurs, notably the apical systolic murmurs, may eventually prove to be due to rheumatic heart disease. There were 4 cases diagnosed as congenital heart disease. Further analysis of the findings in these children would have no bearing on the present theme.

CLINICAL OBSERVATIONS

Two transportation experiments with patients with rheumatic fever have been carried out since 1929. The first, by Coburn,[3] is described in detail in his monograph, and consisted of sending a group of 10 children with rheumatic heart disease, characterized by tenacious activity, from New York to Puerto Rico, to observe the benefits to be obtained by a change of climate. The results were, to quote Coburn briefly, that "the rheumatic process subsided during three months in the Tropics, disappeared clinically during six months in the Tropics, and evidenced itself with sudden reappearance of symptoms in some instances shortly after the return of the patients to New York."

A similar transportation experiment has been in process in the past three winters at Miami Beach under the auspices of T. D. Jones,[4] of

Boston, and C. F. Roche, of Miami Beach. These workers recently related their results, confirming Coburn's good report. Fourteen children with active rheumatic heart disease were sent down from Boston for observation under hospital-solarium management. Two children eventually succumbed, but the others made marked improvement, with gain in weight and loss of clinical symptoms at a rapid pace as the striking features of the experiment. Most of these patients retained their improved state after their return to Boston.

During the past five winter seasons in Miami I have had the opportunity to watch the clinical course of 14 children or young adults with rheumatic heart disease sent down from the North by their physicians. Though a few patients were fairly sick on their arrival, the majority had only slight daily fever or were free of fever before leaving the North, rheumatic activity being indicated only by mild joint symptoms, residual tachycardia, or laboratory findings. Two of this group died, one being a girl of eighteen who suffered attacks of pulmonary edema after coming to Miami and died in a similar attack shortly after returning to New York in the late spring. The other death occurred in a young woman, twenty-one years of age, who remained in Miami two years and had improved enough to undertake light clerical work for nearly a year, only to have a recrudescence of her rheumatic carditis following a "cold," terminating in congestive heart failure and death. Morphological examination of the heart revealed a rheumatic endocarditis involving the mitral and aortic valves, and rheumatic lesions in the myocardium.

A third patient, a Greek girl of seventeen years, apparently developed subacute bacterial endocarditis. She returned North recently, against advice, having stayed in Miami about three months, with some clinical improvement evident the first few weeks.

All of the other patients improved decidedly while in Miami, losing in a few weeks' time, with two exceptions, clinical evidence of an active rheumatic lesion. Gain in weight was pronounced in all but 2 children who failed to eat properly, but even these 2 patients made good progress otherwise. In each instance unless definite fever existed, daily sun baths were instituted routinely. Improvement first showed up by the changed spirit and appearance of the patients. Having had the opportunity of seeing similar cases retain their activity and ill-health over long periods of time when residing in the North, I have been greatly impressed with the giant strides toward normal health taken by the patients in this little group.

One particular patient warrants further comment, owing to the severity of his initial infection. He was the ten-year-old son of a physician in Tennessee. In July of last year he was seized with severe, one might say fulminating, rheumatic fever, with all the classical signs including many rheumatic nodules. A blood culture yielded a growth of

Streptococcus viridans. After three months his symptoms had subsided enough to permit his traveling to Miami. On arrival, a low grade fever and mild joint symptoms persisted, and examination revealed mitral stenosis, cardiac enlargement, anemia, a poor nutrition state, a rapid pulse, and a palpable spleen. There were no residual nodes, no petechiae, no splintering of the nails, no red blood cells in the urine. The question naturally arose as to whether his infection was of subacute bacterial type, but the history of rheumatic nodules seemed to rule out this possibility. (After the first two blood cultures, subsequent cultures were negative.) Although during the first weeks of his stay in Miami the progress of this patient was slow, as soon as it became possible to put him in the sunshine daily he began to pick up in appetite and spirits, lost his joint symptoms and gained 40 pounds in weight. In fact, the weight gain was so rapid that it became necessary to restrict his diet eventually. In spite of the fact that this patient still shows occasional slight elevation of temperature, with a pulse ranging from 84 to 96, I believe his ultimate recovery is certain, provided he escapes reinfection. It is unlikely, in view of the severity of his infection, that he would have made such fine progress had he remained through the winter and spring in the latitude of Tennessee.

In evaluating the effect of the climatic factor on the course of the disease, it should be borne in mind as recently emphasized by Graef[5] and others, that most cases of rheumatic fever tend to subside spontaneously without benefit of specific therapy. However, the *rapidity* with which clinical evidence of rheumatic activity in these patients disappears after arriving in southern Florida is convincing evidence that the removal of such patients to a subtropical climate amounts to "specific therapy."

REVIEW OF LITERATURE

The low incidence of rheumatic fever in tropical countries has been commented upon by many physicians during the past fifty years. Probably the first to emphasize this point was Hirsch,[6] who showed that it was practically absent from tropical countries, except where high plateaus existed. Other early contributions came from Newsholme[7] and Buchanan,[8] the latter showing its rarity in Southern India. During the last ten years renewed interest has developed in the effect of geographical location and climate on the occurrence of rheumatic fever and rheumatic heart disease, and some of the published data will be briefly summarized as follows:

Faulkner and White[9] found by examination of hospital statistics that the incidence of rheumatic fever varied in different localities from 0.2 per cent to 5.8 per cent, with cold, wet climates predisposing to the higher rates. Harrison and Levine[10] concluded from a study of hospital incidence rates that both rheumatic fever and rheumatic heart disease

are more prevalent in northern than in southern cities in the United States. The Seegals[11] showed from hospital statistics that even over a period of years the admission rate of rheumatic fever is greater in the northern than in the southern region of this continent. Davis and Weiss[12] studied a large series of autopsy records in Boston, and after correlating the morphological and clinical data, reported an incidence of rheumatic heart disease of 9.1 per cent.

The incidence of rheumatic heart disease among school children has been commonly stated to be approximately 2 per cent in the United States and England. A recent report from England by McSweeney[13] places the incidence at 1.5 per cent, while surveys of the children in Boston,[14] New York,[15] and Philadelphia[16] showed rates of only 0.66 per cent, 0.89 per cent, and 0.8 per cent, respectively. Naturally the figures vary with the carefulness of the examinations and the inclusiveness of the diagnosis "rheumatic heart disease."

Longcope[17] found the admission rate for rheumatic fever in Johns Hopkins Hospital, Baltimore, was 1.3 per cent, and in commenting on the milder symptoms of the disease in that city as compared to New York, he emphasized the ease of overlooking rheumatic fever in semitropical localities. In several southern states recent surveys have shown a low incidence of rheumatic disease. Stone and Vanzant[18] found a rate of 7.3 per cent among hospitalized patients with heart disease in Galveston, while Schwab and Sculze[19] found a rate of 3.4 per cent among dispensary cardiac patients in the same city. Houston[20] found the incidence of rheumatic fever among hospital admissions in New Orleans to be 0.07 per cent. On the other hand, McLean[21] reported an incidence of rheumatic fever in the Children's Hospital, Birmingham, of 1.8 per cent, with carditis in the majority. He feels that rheumatic heart disease is more common in the South than is generally recognized.

A marked disparity in the incidence of rheumatic fever (including chronic valvular disease and chorea) in different sections of Virginia has quite recently been shown by Wood and Hart.[22] These authors found the incidence among total hospital admissions in Piedmont (central Virginia) more than three times that in Tidewater (eastern Virginia), being 0.48 per cent and 0.15 per cent, respcetively.

Coffen[23] reported the incidence of rheumatic fever in the Pacific Northwest as 0.1 per cent, although 5 per cent of hospital admissions showed rheumatic heart disease. He believes the discrepancy is explained by the migration of persons with previously damaged hearts into that vicinity. In the Rocky Mountain region, 44 per cent of heart disease is of the rheumatic type, according to Viko.[24]

The figures from China have not been very enlightening. Meleney and Kellers[25] found in Northern China frequent instances of mitral stenosis at autopsy, although rheumatic fever was seldom seen. Ander-

son,[26] in Hongkong, found only 5 cases of rheumatic fever or chorea among 3,000 medical admissions to hospitals, yet stated that endocarditis occurred frequently. These discrepancies are probably due to lack of recognition of rheumatic fever in its milder forms, it being rather scantily clad with clinical symptoms. More recently Maxwell[27] has stated that rheumatic fever is absent in the south of China, but more often met with in the northern parts.

In 1930, Clark[28] again proclaimed the rarity of rheumatic fever and rheumatic heart disease in the tropics, stating that during an experience of 33 years in the Malay States he never saw a case of rheumatic fever or chorea, nor did he encounter among 150,000 hospital patients a single instance of mitral stenosis. In addition, he found at autopsy no hearts bearing "the scarred valves of rheumatic disease."

Coburn's[3] monograph in 1931 added considerably to our knowledge of the geographical distribution of rheumatic heart disease. He found Puerto Rico entirely free from clinical rheumatic fever, and is authority for the statement that no gross or microscopic lesions of rheumatic disease were found in nearly 500 autopsies performed by Lambert and Pappenheimer in San Juan, although Koppish encountered 2 cases in necropsy material. Getz, in Panama, is quoted as reporting 5 cases of rheumatic fever in 11,000 hospital admissions yearly, and in addition, finds rare instances of rheumatic carditis at autopsy. By correspondence and direct investigation Coburn gathered data from other countries, showing that the disease is prevalent and severe between latitudes 50 and 40 degrees North diminishing in warmer climates and almost unknown between the Tropics of Cancer and Capricorn, increasing again as cooler climates are reached until it becomes common again between 30 and 40 degrees of latitude South. Thus, in the Eastern Hemisphere it is present in South Africa and Australia, and especially prevalent in Northern Europe, but no tropical place was found in which rheumatic disease is common.

In a report of an investigation for the American Heart Association, Paul[29] has recently summed up the findings regarding the regional distribution and climatic influence on rheumatic fever. "Is it possible," he asks, "that in spite of the conflicting data rheumatic fever may exist insidiously without manifest joint symptoms to give away the diagnosis and that certain climates serve to accentuate the joint symptoms and thus give a false idea of the prevalence of the disease?"

COMMENT

The reason for the absence of rheumatic fever in the tropics is not clear. Most authors believe that the low incidence of upper respiratory infections bears a close relationship to the absence of rheumatic fever. Coburn[3] showed that epidemic upper respiratory infections with *Streptococcus hemolyticus*, common in New York City, are rare in the tropical

environment of Puerto Rico, and that residents in Puerto Rico have an almost constant pharyngeal flora. He feels that the evidence indicates that this is the basic explanation for the rarity of rheumatic fever in Puerto Rico.

Jones and Roche[4] also feel that the absence of respiratory infections has a bearing on the improvement noted in their transportation experiment at Miami Beach, but are convinced that the absence of hemolytic streptococcus is not the essential explanation.

In my opinion, one cannot claim an absence of respiratory infections in southern Florida. The common cold in this climate seems nearly as prevalent as elsewhere, though, on the whole, epidemics of colds and "influenza" in Miami seem mild as compared with those of colder climates. Some idea of the comparative incidence of lobar pneumonia and rheumatic fever was obtained by a previous survey[1] which showed 150 cases of lobar pneumonia in the group of 31,153 hospital admissions that contained only 10 cases of rheumatic fever.

In any event, an inquiry into the prevalence of hemolytic streptococcus in the flora of throats in Miami residents would be enlightening.

It is possible that rheumatic fever is absent in tropical climates because of alterations in the physical chemistry of the human organism, due to the climatic factor, thus creating in the person living in the tropics a poor environment for the infective agent, whatever its identity. It is likely that the student of physical chemistry will eventually explain the impressive immunity against the agent of rheumatic fever with which the tropical resident is endowed.

SUMMARY

1. Only 16 cases of rheumatic fever or chorea occurred among 16,200 medical cases in Miami during a period of eight years.

2. Among 413 patients with organic heart disease seen by the author during the past two years in hospital, clinic, or private practice, 103, or practically 25 per cent were of rheumatic etiology. However, in only 6 instances did the rheumatic disease originate in southern Florida.

3. Rheumatic heart disease is found with only one-third the frequency among elementary school children born in Miami that it is found in children born in the North who have taken up residence in Miami.

4. There is evidence that patients with active rheumatic heart disease improve at a more rapid rate if moved to southern Florida from northern climates during the cold months.

(*For discussion see p.* 117.)

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THE INTERPRETATION OF LEAD INVERSION IN BUNDLE-BRANCH BLOCK*

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IN THE interpretation of electrocardiograms representative of bundle-branch block there is a unanimity of opinion only on the characteristic changes produced within the ventricular complex, but the question as to the branch involved in clinical records is yet a controversial subject. Comprehensive reviews of the problem may be found in the publications of Lewis and Rothschild,[1] Lewis,[2] Fahr,[3] Wilson and Herrmann,[4] Barker,[5] Wilson[6] and their collaborators, and Rothberger.[7] In addition Katz and Ackerman have made the interesting observation that it is possible to transpose the direction of the QRS wave of induced extrasystoles and of experimental right bundle-branch block by changing the position of the dog's heart.[8, 9] Thus the problem has apparently become more complex. We believe these difficulties have been augmented by the fundamental fact that it is very problematical whether conditions existing in disease can be duplicated with sufficient accuracy to allow conclusions to be drawn from the experimental animal. Obviously it would be more satisfactory if the question could be settled on clinical patients without disturbing their existing circulatory state.

A method satisfying the above requirements is suggested by Wiggers' analysis of experimental extrasystoles.[10] In this study it has been shown: (1) that in asychronous excitation of the mammalian ventricle systole of the ventricle first excited precedes systole of the opposite ventricle by a definite and measurable interval; (2) that the opposite ventricle shows a slower tension development, i.e., a prolongation of isometric contraction; and (3) that ejection of the ventricle first stimulated precedes ejection of the opposite ventricle. Thus the basis of the present investigation is that, if the left branch of the bundle of His is interrupted, left ventricular ejection will be retarded due to a delay in arrival of the impulse and longer isometric contraction phase and therefore the subclavian arterial pulse will begin to rise later in relation to ventricular excitation than if the conduction mechanism were normal. A priori if the right branch only is involved, left ventricular excitation and contraction will proceed in a normal manner, and ejection, as indicated by the subclavian pulse, should maintain its usual relation to the beginning of ventricular excitation, as

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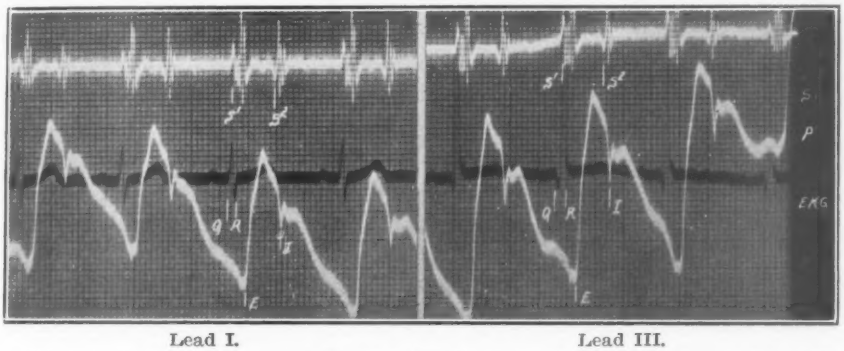
indicated by the QRS of the electrocardiogram. Therefore according to the classical interpretation, the pulse wave of a case with an upright QRS_1 and down QRS_2 (Right BBB) should not be influenced by the bundle-branch block per se, but if the newer conception is correct (Left BBB) there should be a definite delay between the appearance of the QRS in this type of electrocardiogram, and the beginning of the rise of the arterial pulse wave.

METHOD

The electrocardiogram, the subclavian pulse tracing from the left supraclavicular fossa and the apical heart sounds were registered simultaneously. Pulse tracings have been recorded by a Frank segment capsule and sounds by Wiggers' modification of Frank's method.[11] The segment capsules were fixed approximately 92.5 cm. from the recording camera and arranged in such a manner that the middle of the reflecting mirrors, the lens of the projecting microscope of the electrocardiogram and the lens of the camera were in the same horizontal plane. The source of light for the capsules was secured by using an arc equipped with the double-slit mechanism of



Lead I. Lead III.

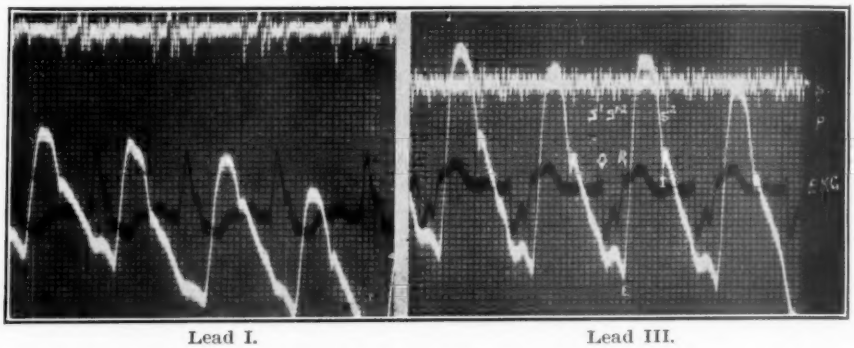
Fig. 1.—Case No. 2172. Lead I: QRS is 0.059 sec. and QE is 0.126 sec. Lead III: QRS is 0.068 sec. and QE is 0.142 sec. Reproduction for effect due to parallax: S, sound wave; P, subclavian pulse tracing; EKG, electrocardiogram.

Katz and Baker[12] which supplies parallel beams. All records were checked for parallax by Garten's method (Fig. 1). No corrections were made when the effect due to parallax was less than 0.004 sec.

After suitable records were secured, lantern slides were made, projected on a screen with a magnification of 10-12× and the required intervals measured on the image with a good celluloid ruler which was graduated in half millimeters. Determinations were made on three cycles in both Leads I and III. All measurements were carried out by one observer. The following intervals were determined: (a) the duration of the main ventricular complex of the electrocardiogram, (b) QE or the interval between the beginning of the QRS and the onset of the cardiac ejection phase as evidenced by the rise of the subclavian pulse tracing, and (c) the isometric contraction phase by Wiggers' method (Wiggers and Clough[13] and Katz and Feil[14]). Occasionally it was impossible to measure the isometric period due to imperfect heart sound records or the presence of a doubled second sound. In five of the cases of bundle-branch block the first sound was definitely "reduplicated" or "split," but as Lewis has previously reported,[15] the first component of the "reduplicated" sound preceded the onset of ventricular excitation and could therefore hardly be attributed to asynchronous systole of the ventricles. In such cases we have arbitrarily taken

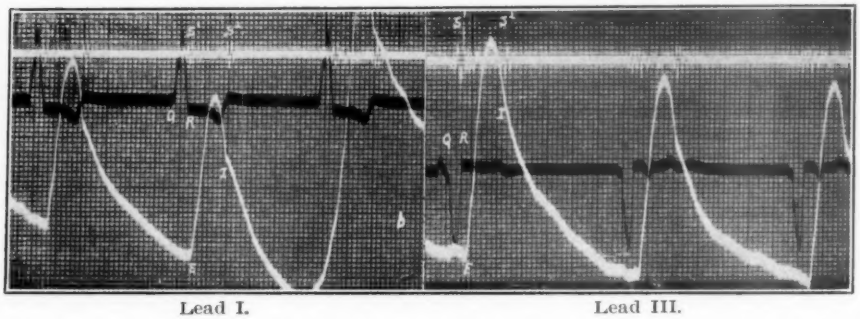
the beginning of the second component as indicating the onset of ventricular contraction. We believe the error of a single measurement is perhaps not considerably over 0.004 sec.

The most pronounced doubling of the first sound occurred in a case with a P-R interval of slightly more than 0.20 sec. In Case 2206 (Fig. 3) which showed a complete A-V block and ventricular complexes typical of the usual type of bundle-branch block, the first sound varied in intensity with the P-QRS relations and, in addition, there appeared to be a critical As-Vs interval at which doubling of the first sound appeared. These observations would lend no support to a theory that the first component of the doubled sound is caused by ventricular contraction. It probably occurs frequently in bundle-branch block because of the relations of atrial



Lead I. Lead III.

Fig. 2.—Case No. 2276. Lead I: QRS is 0.160 sec. and QE is 0.176 sec. Lead III: QRS is 0.163 sec. and QE is 0.181 sec. Double first sound, S^1 and $S^{1, 2}$



Lead I. Lead III.

Fig. 3.—Case No. 2206. Lead I: QRS is 0.127 sec. and QE is 0.175 sec. Lead III: QRS is 0.131 sec. and QE is 0.172 sec. The QRS in Lead II is distinctly notched

and ventricular systole, the mechanism being similar to that present in complete A-V block in which atrial sounds are heard.

No attempt was made to determine the speed of the pulse wave, and in the absence of any gradient for velocity and the impossibility of obtaining the distance of the arterial system involved, we know of no way by which this could be evaluated. It seems probable, however, that any modifying influence from this source would tend to shorten the QE, as our patients with bundle-branch block were over fifty years of age, all but one had an arterial hypertension, and there were definite, though moderate, sclerotic changes in the palpable arteries in all. Some of the pathological controls were in a circulatory state similar to that in the cases of bundle-branch block, yet the QE in the former cases were not significantly different from the average found in their own group. Also if the accepted standards for pulse wave

velocity[16, 17, 18, 19] are taken as indicating the velocity of the pulse wave in the aorta, it would be necessary to show a tremendous decrease in these figures in order to secure a time interval sufficient to explain the increased QE found in our cases of bundle-branch block.

RESULTS

The intervals previously described, QRS, QE and the isometric period were measured in (a) eighteen normal individuals, (b) seven cases of bundle-branch block in which the QRS was upright in Lead I and downward in Lead III, (c) twenty-two cases with various types of heart disease but with a normal duration of ventricular excitation, and (d) nine cases of heart disease with a prolonged period of ventricular excitation but in which the electrocardiogram was not typical of bundle-branch block.

TABLE I

NORMAL CONTROLS

NUMBER	QE		ISOMETRIC PERIOD	VENTRICULAR RATE
	LEAD I	LEAD III		
1957	0.132 sec.	0.114 sec.	0.069 sec.	70
1994	0.142	0.151	0.065	94
2017	0.119	0.137	0.046	75
2021	0.127	0.127	0.064	72
2026	0.149	0.138	0.070	70
2060	0.119	0.129	0.058	72
2064	0.145	0.134	0.040	52
2065	0.129	0.113	0.065	75
2077	0.151	0.124	0.045	60
2078	0.166	0.163	0.082	75
2080	0.147	0.141	0.071	75
2081	0.134	0.148	0.046	68
2091	0.137	0.153	0.063	60
2172	0.126	0.142	0.050	75
2188	0.134	0.134	0.077	75
2183	0.129	0.114	0.027	66
2184	0.119	0.119	0.036	75
2028	0.120	0.118	0.048	94

The QE values for the eighteen normal individuals of Group A are given in Table I. Fig. 1 is the record from one such case. These individuals were young males between the ages of twenty and thirty years who were leading vigorous lives and who showed no evidence of car-

TABLE II

BUNDLE-BRANCH BLOCK

NUMBER	QE		ISOMETRIC PERIOD	VENTRICULAR RATE	ARTERIAL PRESSURE	AGE
	LEAD I	LEAD III				
1954	0.163 sec.	0.165 sec.		72	180/112	69
2020	0.195	0.169	0.048 sec.	76	190/126	62
2069	0.182	0.173	0.097	100	170/100	53
2155	0.152	0.162	0.042	94	195/100	57
2229	0.173	0.168	0.080	92	144/96	68
2206	0.175	0.172		65	168/58	53
2294	0.193	0.176	0.090	100	112/86	60

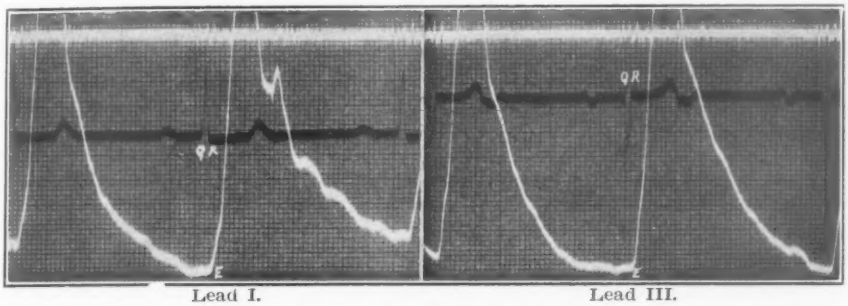
TABLE III

PATHOLOGICAL CONTROLS

NUMBER	QE		ISOMETRIC PERIOD	VENTRICULAR RATE	ARTERIAL PRESSURE	AGE	CLINICAL DIAGNOSIS
	LEAD I	LEAD III					
1996	0.086 sec.	0.098 sec.	0.026 sec.	75	110/70	22	Diphtheretic Myocarditis (?).
2048	0.101	0.125		90	130/30	48	Aortic Insufficiency (Luetic).
2054	0.105	0.126	0.039	72	138/90	43	Aortic Aneurysm (Luetic).
1943	0.135	0.138		78	106/78	13	Rheumatic Heart Disease. Mitral Insufficiency.
2032	0.146	0.147	0.056	80	118/90	34	Aur. Fib. Rheu. H. D. Adherent Pericardium (?).
2094	0.132	0.145	0.075	88	106/58	15	Rheumatic Heart Disease. Mitral Stenosis.
2100	0.148	0.148	0.048	94		23	Rheumatic Heart Disease. Mitral Stenosis.
2105	0.112	0.119	0.065	100	110/54	12	Rheumatic Heart Disease. Mitral Stenosis.
2154	0.110	0.115	0.056	100		7	Rheumatic Heart Disease.
2052	0.096	0.084	0.027	124		57	Rheumatic Heart Disease. Aortic and Mitral Stenosis Insufficiency.
2217	0.105	0.116		75	100/70	26	Congenital Heart Disease.
2114	0.116	0.118	0.036	60		9	Congenital Heart Disease.
2045	0.129	0.087	0.027	110	132/86	37	Cardiac Neurosis (?).
2056	0.088	0.092	0.036	140	140/82	14	Exophthalmic Goiter.
2116	0.139	0.144	0.053	75	128/82	24	Paroxysmal Tachycardia.
2171	0.095	0.097	0.038	94	154/72	52	Thyrotoxicosis. Myocardial Disease.
2189	0.099	0.103	0.031	116	152/60	18	Exophthalmic Goiter.
2189	0.127	0.133	0.040	138			Post-thyroidectomy.
2050	0.098	0.115	0.028	96	126/72	52	Arteriosclerotic Heart Disease.
2057	0.113	0.123	0.063	100	158/90	55	Arteriosclerotic Heart Disease.
2075	0.123	0.142	0.066	60	128/96	39	Arteriosclerotic Heart Disease.
2185	0.135	0.141	0.089	68	135/94	23	Hypertensive Heart Disease.
2074	0.116	0.099		34	160/58	68	Arteriosclerotic Heart Disease.

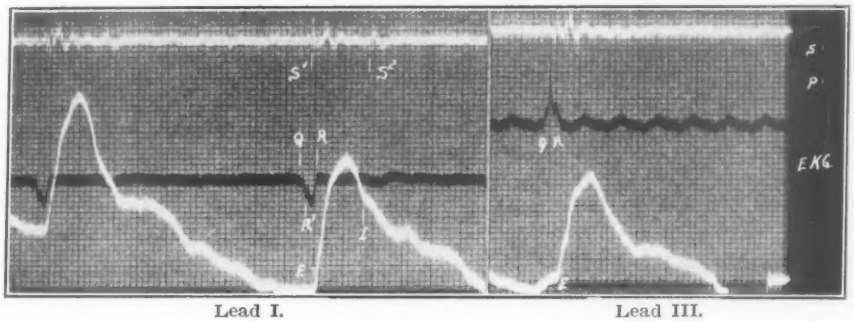
diac or vascular disease. The electrocardiogram in all cases was normal and the QRS varied from 0.049 to 0.093 sec. The arithmetic mean for QE is 0.1347 sec. in Lead I and 0.1333 sec. in Lead III. The corresponding standard deviations of the means are 0.003567 and 0.00348 sec.

The findings in seven cases of bundle-branch block (Group B) appear in Table II. Fig. 2 is the record of one of these. All the individuals in this group had arteriosclerotic heart disease, with varying degrees of cardiac hypertrophy which was preponderantly of the left ventricular type. With one exception all these tracings would un-



Lead I. Lead III.

Fig. 4.—Case No. 2074. Lead I: QRS is 0.087 sec. and QE is 0.116 sec. Lead III: QRS is 0.069 sec. and QE is 0.099 sec.



Lead I. Lead III.

Fig. 5.—Case No. 1992. Lead I: QRS is 0.104 sec. and QE is 0.098 sec. Lead III: QRS is 0.114 sec, and QE is 0.109 sec.

questionably be labelled as bundle-branch block, i.e., a supraventricular QRS more than 0.10 sec. in duration, opposite in direction in Leads I and III, with a distinct notch in the main ventricular complex and with T-waves opposite in direction to the QRS. Case 2206 (Fig. 3) probably represents a nodal rhythm but the QRS and T-waves are uniform and satisfy the remaining requirements for bundle-branch block. This case therefore has been included with the above group, representing the usual type (Right BBB, old terminology). The arithmetic mean for QE in the group is 0.1761 sec. in Lead I and 0.1693 sec. in Lead III. The corresponding standard deviations for the means are 0.0058 and 0.0018 sec.

The determinations on the group of controls with heart disease (Group C) are given in Table III. The duration of QRS was less than 0.10 sec. in all leads. The analysis of these pathological cases would be of greater value if they could be grouped according to age or type of heart disease. Unfortunately our clinical material was too small for this purpose. Fig. 4 is a record illustrating the normal time relations of the subclavian pulse in a case with a marked left ventricular preponderance and a 2:1 A-V block. The arithmetic mean for QE in the group is 0.1154 sec. in Lead I and 0.1198 sec. in Lead III. The corresponding standard deviations for the means are 0.00383 and 0.00426 sec.

No attempt was made to analyze statistically the findings in the cases with a prolonged period of ventricular excitation (Group D). Some of these records were very suggestive of bundle-branch block but have not been included in that group because the QRS were not entirely typical. Fig. 5 is of interest because of its relation to the unusual type of bundle-branch block. T-waves are not present and the ventricular rate is 33, but the QRS is definitely notched, widened and downward in Lead I and upright in Lead III. The ventricular excitation wave in this case is therefore much the same as that present in the unusual type of bundle-branch block (Left BBB, old terminology). The QE is 0.098 sec. in Lead I and 0.109 sec. in Lead III, and these values fall within the limits of Group C.

DISCUSSION

What effect has the aberrant path of the excitation wave on the mechanics of ventricular systole in clinical bundle-branch block? Wiggers in his study of artificially induced extrasystoles concludes: "When a local artificial stimulus is applied to any portion of the ventricular surface, the impulse spreads somewhat radially from the point of stimulation and induces a series of local fractionate contractions responsible for the initial slow rise of intraventricular pressure. This continues until the impulse has reached the His-Tawara system and has been conducted by that system to the unexcited portions of the ventricle. Consequently, two different contraction processes almost imperceptibly merge, viz., (a) a localized fractionate contraction occasioned by a relatively slow fiber-to-fiber excitation, and (b) a more generalized contraction of the remaining ventricle excited via bundle branches in more rapid sequence. Inasmuch as the latter also starts in a fractionate manner isometric contraction and total systole are prolonged."[10] It is probable that this same process is present in bundle-branch block due to the fiber-to-fiber conduction of the excitation wave before it reaches the distal portions of the bundle branch which is blocked. The statistical analysis of the isometric periods in the cases of bundle-branch block is not conclusive because of the small number, but it indicates that the mean of the isometric periods in our cases

of bundle-branch block is not significantly different from that of the normal group. Thus after the excitation wave reaches the terminal portions of the His-Tawara system, ventricular systole probably progresses in a normal manner, and the delay in the incidence of the subclavian pulse is probably due to the decreased speed and lengthened path of the excitation wave as it is conducted through or around the interventricular septum. The analysis of our cases shows that the beginning of the rise of the subclavian pulse occurred, on an average, definitely later in individuals with the usual type of bundle-branch block (Right BBB, old terminology) than in normal individuals or in patients with heart disease but with a normal duration of ventricular excitation. This result is statistically significant when tested by the method of Fisher.[20] Also in one instance in which the QRS was widened, notched and downward in Lead I and upright in Lead III, the value for QE was within the limits of QE for the group with heart disease but with a normal duration of ventricular excitation. If the left ventricle in our cases of bundle-branch block was stimulated in a normal manner, then we are unable to explain the increase in the value of QE, which amounts to, in an average, 0.0414 sec. as compared to the normal, or 0.0607 sec. as compared to the pathological controls. But, if these cases represent a left bundle-branch block, the increased value for QE becomes readily explainable by the aberrant path of the excitation wave. We believe therefore that the left ventricle is activated last in the usual type of bundle-branch block. This is in accordance with the original idea of Fahr and the more recent conclusion of Wilson and Barker.

CONCLUSIONS

A new method of attacking the problem of bundle-branch block has been described.

In our cases of bundle-branch block with an upright QRS_1 and downward QRS_3 the incidence of the subclavian pulse was definitely delayed. Therefore it seems most probable that this type of electrocardiogram represents a left rather than a right bundle-branch block.

I wish to express my indebtedness to Dr. R. Dominguez for useful criticism and for the statistical analysis of the data. Dr. Harold Feil has given me the opportunity to study one of his cases and has offered numerous suggestions as to the technic employed. Dr. Carl J. Wiggers has kindly and critically reviewed the technic and the manuscript.

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COMPLETE HEART-BLOCK IN HYPERTHYROIDISM FOLLOWING ACUTE INFECTIONS: A REPORT OF SIX CASES WITH NECROPSY FINDINGS IN ONE CASE*

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THE high incidence of irregular cardiac action is one of the striking features of hyperthyroidism. The arrhythmia consists mainly of auricular fibrillation, however, either paroxysmal or permanent, and to a less extent, of auricular flutter. These forms of arrhythmia depend on disturbance of auricular contractility. Defective auriculoventricular conductivity is much less frequent, and complete auriculoventricular dissociation is uncommon. In a review of the literature on the etiology of heart-block and on arrhythmia occurring with hyperthyroidism, we could find only four reports of complete heart-block associated with hyperthyroidism. Merklen,[11] in 1882, reported the case of a woman, aged twenty-seven years, who had had exophthalmic goiter for six years, and who had attacks of ventricular standstill of four or five seconds' duration with convulsive seizures. These attacks had developed eight days following an acute cold, with sore throat. There also was fever which could not be explained by the physical findings. The seizures occurred repeatedly over a period of two days, and their cessation was associated with recovery from the arrhythmia. In 1915 de Vries Reilingh[14] reported a case of Basedow's disease with heart-block and Stokes-Adams syndrome, in which the cardiac action returned to normal within ten days. Dameshek,[4] in 1924, in an analysis of the instances of arrhythmia reported in a series of 141 cases of hyperthyroidism, found electrocardiographic evidence of complete auriculoventricular dissociation in two cases: that of a woman, aged twenty-six years, and that of a man, aged twenty-nine years.

Reports of less severe degrees of defect in conduction have been somewhat more numerous. Lewis,[10] in 1913, referred to a patient with a history of repeated attacks of rheumatic fever, who had partial heart-block following thyroidectomy for exophthalmic goiter, and, subsequently only prolonged auriculoventricular conduction time. Krumbhaar[9] noted two cases in which the P-R interval was prolonged, in a series of fifty-one cases studied. Willius, Boothby and Wilson,[17] in a study of a series of 298 cases, found one in which there was a P-R interval of twenty-eight hundredths of a second. In the study made by Dameshek[4] in 1924 there were, besides the two cases of com-

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plete heart-block, two cases in which conduction time was delayed. In 1929 Andrus,[1] in a series of eighty-six cases of exophthalmic goiter and adenomatous goiter with hyperthyroidism, found one case of heart-block, the type of which he did not specify. Eason,[5] in 1930, described the case of a young woman who had exophthalmic goiter, and who had fever of several weeks' duration following tonsillectomy; subsequent to the febrile period, a syncopal attack, with associated arrhythmia, occurred. The electrocardiogram gave evidence of partial heart-block; that is, a prolonged P-R interval with occasionally dropped ventricular complexes. The patient recovered satisfactorily from the arrhythmia. Cameron and Hill,[3] in 1932, reported two cases of partial heart-block in association with exophthalmic goiter; the patients were young women. In one case the heart-block was present three weeks following an attack of tonsillitis; in the other case the heart-block developed twenty-four days following the onset of acute tonsillitis and four days following tonsillectomy. The authors called attention to the possibility of the infection of the throat being an etiological factor in the production of the heart-block.

Investigators, as follows, have reviewed series of cases of hyperthyroidism and have not found evidence of disturbed auriculoventricular conductivity: Smith and Colvin,[13] 100 cases; White and Aub,[16] twenty-seven cases; Kerr and Hensel,[8] fifty-eight cases. The experience of Goodall and Rogers,[6] however, was at variance with these findings; they found the P-R interval to be prolonged in 242 cases in a series of 787 cases of hyperthyroidism which they studied. There was, however, no instance of a higher grade of defect in conduction.

The cases in which electrocardiograms made at The Mayo Clinic since 1923 gave evidence of complete heart-block were reviewed. Six of the patients had exophthalmic goiter. No cases of adenomatous goiter with hyperthyroidism in which complete heart-block occurred were found in this period of time. This was contrary to expectation when the study was undertaken. We had anticipated a coincidental association of complete heart-block resulting from arteriosclerotic heart disease and hyperthyroidism and also that this association would occur less frequently with exophthalmic goiter than with adenomatous goiter with hyperthyroidism, since the latter occurs at a more advanced average age.[2]

REPORT OF CASES

CASE 1.—A woman, aged twenty-two years, came to the clinic September 13, 1924, with exophthalmic goiter of one and a half years' duration. She had not received digitalis. On account of a mild, acute infection of the upper part of the respiratory tract, operation was delayed until September 30, when subtotal thyroidectomy was performed. Except for persistent fever until the eighth postoperative day, convalescence was uneventful. On that day an epileptiform seizure suddenly developed and was accompanied by marked bradycardia. The attacks recurred for two

days, and repeated electrocardiograms gave evidence of complete auriculoventricular dissociation. Conduction time became normal October 17, and subsequently the patient's convalescence was without noteworthy incident. Two years later she reported that she was in good health.

CASE 2.—A woman, aged twenty-seven years, came to the clinic September 13, 1922, on account of severe exophthalmic goiter of five months' duration. October 3 the left superior thyroid vessels were ligated, and October 10 the corresponding vessels on the right side were ligated. The patient did not return for further operation until February 22, 1923. Three days after her return acute follicular tonsillitis with fever developed; it persisted for five days. Partial thyroidectomy was performed March 17. The postoperative reaction was rather severe, the pulse was persistently rapid, and the temperature was elevated until the eighth postoperative day, when the pulse rate suddenly dropped from 140 to 72, and to 36 the following day. A syncopal attack occurred on that day, with unconsciousness of a few seconds' duration; there was marked pallor, but no convulsion or muscular twitching. Fifteen such attacks occurred during the day. The electrocardiogram revealed complete auriculoventricular dissociation. Normal conduction time was not established until six days later. Twenty-five days following thyroidectomy the patient was dismissed from observation, and three months later she reported that she was in good health.

CASE 3.—A man, aged thirty-five years, came to the clinic March 11, 1925, on account of severe exophthalmic goiter of one year's duration, and mild congestive heart failure. An electrocardiogram revealed rapid auricular fibrillation. Four days later scarlet fever developed, and the temperature was elevated for four days. March 29 the fever recurred, and there was evidence of multiple arthritis. March 31 the pulse became regular and its rate dropped abruptly to 40 each minute. The patient appeared to be extremely ill but he did not lose consciousness. April 1, an electrocardiogram gave evidence of a ventricular rate of 47 and of auricular fibrillation with regular ventricular rhythm. The QRS complex represented an interval of twelve-hundredths of a second. The pulse remained regular; its rate was between 40 and 47 for three days and then gradually increased and again became irregular. April 9, the QRS complex represented an interval of normal duration. May 18, the right lobe of the thyroid gland was removed. A severe reaction followed, but there was no evidence of recurrence of the heart-block.

CASE 4.—A woman, aged fifty-three years, came to the clinic January 21, 1923, with exophthalmic goiter of ten months' duration. The basal metabolic rate was +49 per cent. She had not received digitalis or iodine. A week later an acute infection of the upper part of the respiratory tract, with acute tonsillitis and fever, developed. This persisted for a week. For a month she complained of a cold, but there were no findings to substantiate the complaint. The fever recurred March 4, but the physical findings were still negative. March 6 the pulse rate suddenly dropped from 116 to 70, and the patient became weak and nauseated, and vomited. An electrocardiogram revealed complete auriculo-ventricular dissociation, and this was found again March 7 (Fig. 1).

The patient died March 10. The post-mortem findings were as follows: the heart weighed 257 gm. and was not enlarged. Nothing unusual was noted about the epicardial surfaces. The endocardial surfaces were smooth, and everywhere intact. There were no gross lesions of the valve leaflets, cusps, or chordae tendineae. The walls of the ventricles were of normal thickness. The left ventricle was thought to be slightly dilated. On cut section the myocardium was normal in color and consistence.

Sections were taken from various portions of the heart for microscopic study. Sections taken from the walls of the auricles, and in the region of the sino-auricular node, appeared normal and stained well. Sections taken from different portions of the wall of the left ventricle appeared normal. Sections taken through the auriculoventricular node and bundle contained, especially in the ventricular portion

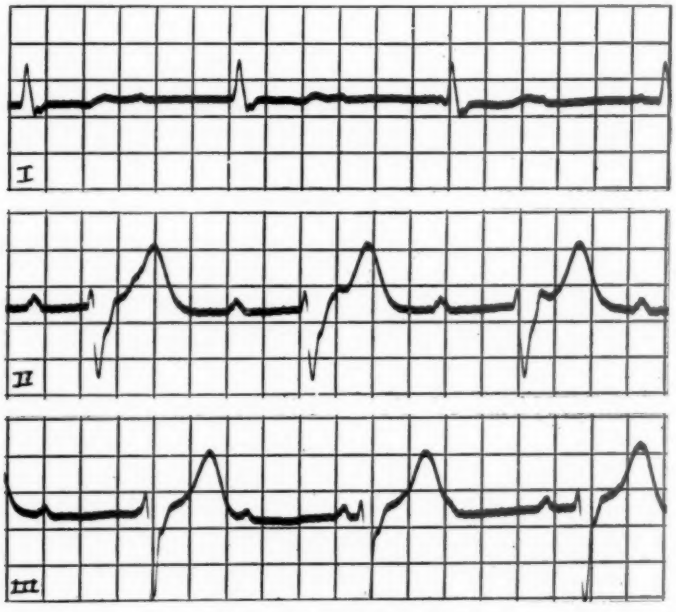

Fig. 1.—Complete auriculoventricular dissociation. Ventricular rate 50 beats a minute; auricular rate, 110.

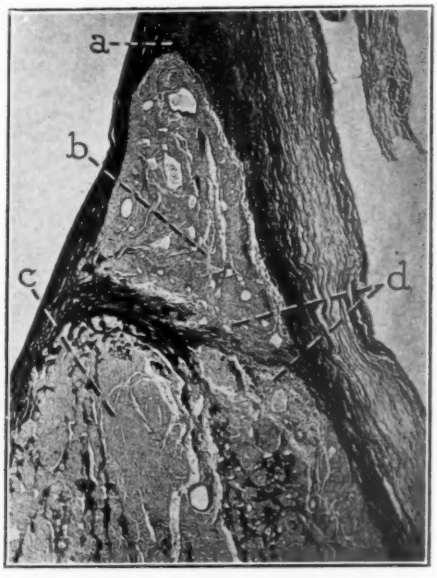

Fig. 2.—*a*, Membranous portion of the interventricular septum; *b*, auricular ventricular bundle; *c*, muscular portion of interventricular septum; *d*, areas of cellular infiltration (×35).

of the bundle, and also in adjacent structures, extensive cellular infiltration (Fig. 2). This process consisted of cellular foci composed of numerous polymorphonuclear leucocytes (Fig. 3), and considerable numbers of small mononuclear cells. Many dilated blood vessels were present. This portion of the auriculoventricular bundle and the adjacent tissues were somewhat edematous. The cellular infiltration was most marked at the juncture of the membranous with the muscular portion of the interventricular septum. The infiltration extended for a considerable distance down into the interventricular septum. There were several regions of leucocytic infiltration throughout the wall of the right ventricle.

In sections taken at the juncture of the membranous and muscular portions of the interventricular septum, where the leucocytic infiltration was most extensive, and stained with Brown Gram stain, were some gram-positive bacteria (Fig. 4), which were believed to be either diplococci, or streptococci in short chains. These bacteria were found in the ventricular portion of the auriculoventricular bundle and its adjacent structures. They were most numerous just beneath the endocardium.

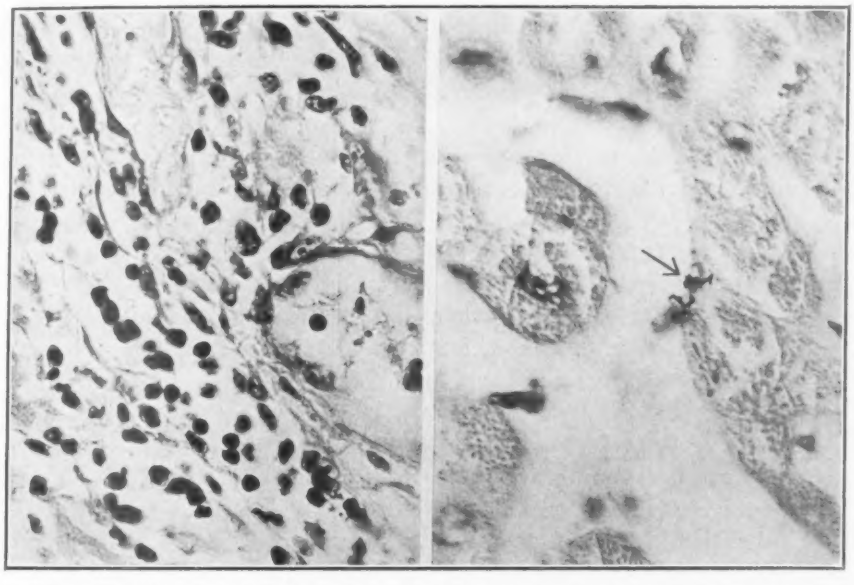

Fig. 3.—Higher magnification of a section taken from area *d* in Fig. 2. Numerous polymorphonuclear leucocytes, a few small mononuclear cells, and many dilated blood vessels and considerable edema, are evident. Hematoxylin and eosin (×700).

Fig. 4.—Section taken from area *d* in Fig. 2, stained with Brown Gram stain. The arrow points to what is believed to be a short chain of streptococci (×500).

The thyroid gland weighed 58 gm., and on microscopic examination was seen to have undergone rather marked parenchymatous hypertrophy. The thymus was moderately hypertrophied. The liver was somewhat atrophic; its weight was 1,284 gm. Other structures examined were essentially normal.

CASE 5.—A woman, aged sixty-three years, came to the clinic June 12, 1929, on account of exophthalmic goiter of two years' duration. She also had mitral stenosis. She had received digitalis continuously for five months, until the time of her admission to the clinic. She had congestive heart failure, and the electrocardiogram gave evidence of complete auriculoventricular dissociation. There was no history or evidence of recent acute infection. Administration of digitalis was discontinued, and two weeks later conduction time was normal. August 7 lobectomy was per-

formed. Six months later the patient was reexamined; the P-R interval was then twenty-eight hundredths of a second, and the basal metabolic rate was −11 per cent.

CASE 6.—A woman, aged sixty-five years, came to the clinic February 19, 1929, on account of exophthalmic goiter. She had received digitalis continuously for four months, to the time of her admission at the clinic; we found that she had complete heart-block. Administration of digitalis was discontinued, and five days later there was a regular ventricular response to auricular contraction. However, there was delayed auriculoventricular conduction time, and this persisted. Subtotal thyroidectomy was performed March 6. An electrocardiogram, made seven days later, disclosed normal conduction time.

In all of the six cases reported, the Wassermann test was negative, and in Cases 1, 2, 3 and 4 throat cultures for *Corynebacterium diphtheriae (Bacillus diphtheriae Klebs)* were negative.

COMMENT

Judging from any evidence which we were able to find concerning either the morbid anatomy or functional disturbance of the heart in the presence of hyperthyroidism, there would seem to be no reason for hyperthyroidism in itself to result in interference with auriculoventricular conductivity. No distinctive type of cardiac lesion has been accepted generally as characteristic of hyperthyroidism. That nonspecific myocardial lesions occur more frequently and are of greater extent in cases of hyperthyroidism than in control series has been observed repeatedly in the study of the pathological changes in the heart in cases of hyperthyroidism.[12, 15] In exceptional cases there are regions of mononuclear infiltration and destruction of muscle fiber, which, if situated in or near the bundle of His could result in loss of auriculoventricular conductivity.

Ordinarily, in cases of hyperthyroidism, there is no definite change in auriculoventricular conduction time, in spite of the accelerated cardiac rate and the stimulated general physiological activity. Although there has been some divergence of opinion concerning the length of the P-R interval in the presence of hyperthyroidism, Joll[7] concluded, after a review of the published evidence, that there is no shortening of the auricular period and that in a few cases there may even be a degree of heart-block. In the reported cases to which he referred, however, there was no evidence to indicate that in those cases in which the interval was increased, hyperthyroidism was the only etiological factor. In each of the first four cases reported in the series of six reviewed from the records of The Mayo Clinic, an acute infection immediately preceded or accompanied the onset of the heart-block. In Case 4, the pathological findings were conclusive evidence of the mode of production of the heart-block, and were indicative of the disturbance of mechanism in Cases 1, 2 and 3, in all of which the sequence of events preceding the onset of the heart-block was similar. In Case 3, the clinical course of the patient subsequent to recovery from the heart-block also would tend to indicate the presence of a localized inflammatory lesion in or near the auriculoventricular bun-

dle, secondary to scarlet fever. The patient gradually recovered from the heart-block without any appreciable decrease in the severity of the hyperthyroidism, and later, following lobectomy and a severe postoperative reaction evidence of recurrence of defective auriculoventricular conductivity did not develop.

The part played by acute infection in the production of interference with auriculoventricular conductivity has been thoroughly established by extensive investigations of the pathological anatomy. In the literature are reports of numerous cases in which the development of heart-block has been conclusively explained by the presence of localized inflammation, of various degrees, in the auriculoventricular bundle or adjacent to it. Such processes have accompanied infections of many types, such as tonsillitis, rheumatic fever, diphtheria, pneumonia, gonorrheal septicemia, and infection of the blood stream from various sources. At least four of the reported cases of hyperthyroidism with associated heart-block referred to in the literature, namely, those of Merklen,[11] Eason,[5] and Cameron and Hill,[3] would seem to fall into the same category as the first four cases of the series which we have reported in this paper, so far as recent infection is concerned. In the cases brought to attention by Eason, and by Cameron and Hill, the patients had had acute tonsillar infection, and in the case referred to by Merklen an acute infection of the upper part of the respiratory tract shortly preceded the onset of the heart-block. Furthermore, in all of these cases the patients were young, and gave no evidence of having suffered previous cardiac injury.

With exophthalmic goiter, the patients display a pronounced susceptibility to acute tonsillitis, and although most of them recover promptly and satisfactorily from the infection, at times the reaction is severe. It would seem possible that fatigue from overwork, or perhaps an intrinsic metabolic disturbance, would result in lowered resistance to metastatic infection or toxemia, with greater susceptibility to such complications as developed in Case 4 of those here reported. This explanation has been suggested by Rake and McEachern.[12] Yater[18] stated that rabbits given injections of thyroxine are more susceptible to infection, that focal necrosis readily develops throughout the heart, and that other lesions indicating inability of the myocardium to cope with infection appear in cases of hyperthyroidism.

The occurrence of auriculoventricular dissociation in Case 5 is reasonably explained on the basis of the effect of digitalis on a previously injured auriculoventricular bundle. Chronic mitral valvular disease was present in this case, and administration of digitalis for a month resulted in complete auriculoventricular dissociation, which disappeared following discontinuance of the treatment with digitalis. The probability that the bundle had been injured prior to the time of

the treatment with digitalis is enhanced by the fact that seven months after occurrence of the auriculoventricular dissociation, conduction time was slightly prolonged at the time when the low basal metabolic rate, previously mentioned, was determined. In Case 6, although no clinical evidence of intrinsic cardiac injury was present, the age of the patient made probable the same explanation as applies in Case 5. In Case 6 the patient had taken digitalis continuously for five months prior to examination at the clinic and when administration of digitalis was discontinued, the heart-block decreased in severity, although it was not known that it subsided until following thyroidectomy.

SUMMARY

Six cases of exophthalmic goiter in which complete auriculoventricular dissociation occurred were observed at The Mayo Clinic. Three of the patients had had acute tonsillitis shortly preceding the onset of the arrhythmia and one patient had had scarlet fever. In the one fatal case, necropsy revealed an inflammatory lesion involving the region of the bundle of His, in which we were able to demonstrate gram-positive bacteria which we believed to be either diplococci or streptococci in short chains. In the two cases of the series in which development of the heart-block was not associated with acute infection, there is reason to believe that the heart-block was precipitated by the effect of digitalis on a previously injured auriculoventricular bundle. In those cases in which acute infection was present, evidence is advanced to indicate that the hyperthyroidism predisposed the patient to the development of acute infection, and also to secondary myocardial involvement which resulted in the occurrence of heart-block.

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Department of Clinical Reports

STOKES-ADAMS DISEASE TREATED WITH EPHEDRINE; FINAL REPORT OF A CASE*

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IN 1928 one of us[6] reported in this JOURNAL a case of Stokes-Adams disease with complete cessation of attacks after the use of ephedrine by mouth. The patient was further observed by us up to the time of his death October 20, 1932. A review of the case with the necropsy findings is given here.

Summary of first admission: J. M., a sixty-five-year-old white laborer, was admitted to the Medical Service at City Hospital, September 27, 1927, complaining of fainting attacks. His present illness began eight days before admission when he suddenly became dizzy and fainted. Recovery was prompt and complete, but similar attacks recurred with increasing frequency and on admission were occurring at intervals of several minutes. His past history was essentially negative. There was no history of diphtheria or syphilis. The patient was accustomed to heavy work and had been a hard drinker. Physical examination revealed a well-nourished and well-developed adult male, resting comfortably in bed. He was having frequent attacks which lasted from fifteen to twenty seconds, in which he showed mental confusion and inability to talk. His face assumed a staring expression, and there was loss of consciousness followed by convulsions. During the attacks his skin became blanched and there was complete cessation of heart sounds, cardiac activity and peripheral pulses. The heart action was resumed with a powerful precordial heave, a distinct flushing of the skin and a sudden return of consciousness. The pulse rate after the attacks was 24 per minute. The chest was emphysematous and the apex impulse could not be definitely localized at any time. The heart sounds were loud and of good quality, and there was a systolic murmur at the apex. Blood pressure was 140/56 mm. Blood Wassermann reaction was negative.

Electrocardiograms taken on admission during one of his attacks showed consecutive periods of ventricular asystole of 7.4 seconds, 3.4 seconds and 10.2 seconds. Later cardiograms taken after the patient had been given ephedrine showed left ventricular preponderance, complete heart-block with regular rhythm. Ventricular rate 25; auricular rate 58 per minute.

Course: The patient was first treated with 10 minims (0.6 c.c.) of 1:1000 solution of epinephrine subcutaneously during attacks. This gave him relief for several hours. Thirty mg. of barium chloride were given three times a day for six days, but this was discontinued because of lack of appreciable effect. He was then given 30 mg. of ephedrine sulphate three times daily by mouth. This gave him relief from the attacks, and in one week the individual dose was cut to 20 mg. He had no more attacks and in two weeks the medication was discontinued. The patient remained symptom free during the ensuing ten weeks and was discharged.

*From the Medical Clinic of Western Reserve University at Cleveland City Hospital.

Subsequent course: The patient was next seen by us in September, 1928, when he returned to the hospital because of a recurrence of his attacks and on admission showed essentially the same picture as on the previous admission. The medication consisted of 30 mg. of ephedrine hydrochloride three times daily by mouth. There was relief of the symptoms and the patient was discharged on this dosage and followed in the Out-Patient Department until May, 1932, when he was readmitted to the Medical Service, complaining of loss of vision.

Physical examination at this time showed a senile white male who was not acutely ill. Both eyes showed opacities of the lens. There was marked dental caries. The pharynx was normal and the tonsils were atrophic. The thyroid was not palpable. The chest was emphysematous and the breath sounds were normal. No râles were heard. The left border of cardiac dullness was 8 cm. from the midsternal line and no murmurs were heard. There were occasional extrasystoles. The

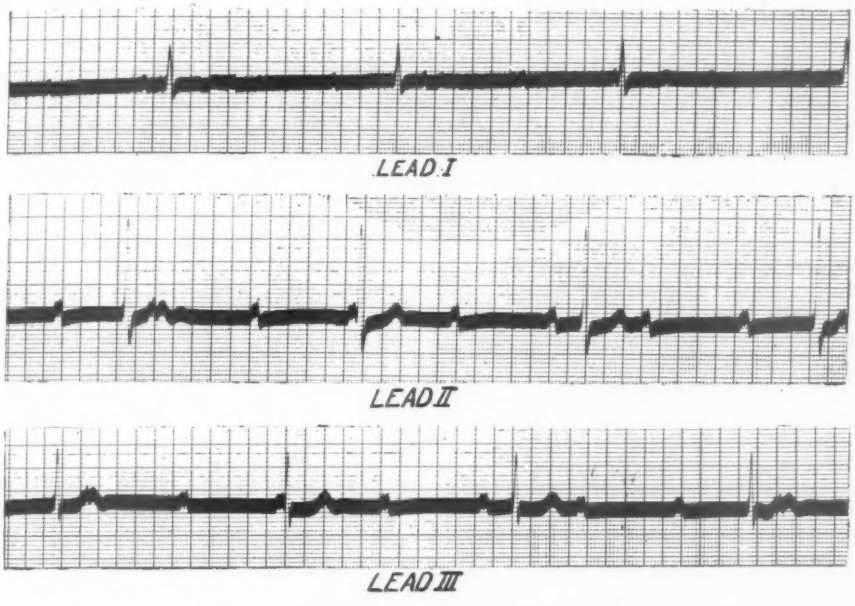

Fig. 1.—Electrocardiogram taken May 26, 1932, showing complete heart-block. Auricular rate 60, ventricular rate 25.

pulse rate was about 26 per minute. Blood pressure was 130/54 mm. The patient showed no signs of cardiac failure. The peripheral vessels were markedly sclerotic. The reflexes were physiological.

Electrocardiograms taken May 26, 1932, showed complete heart-block. The T-wave was upright in all leads. There was no prolongation of the QRS interval. Auricular rate 60, ventricular rate 25 per minute (Fig. 1).

Course: The patient was given 30 mg. of ephedrine sulphate daily. On this dose he was apparently free from attacks and the heart rate remained at about 26 per minute. He was transferred to the Ophthalmological Service and an iridectomy of the right eye was done August 12. One week later he had several attacks and the dose of ephedrine was raised to 25 mg. twice daily. This seemed to control his symptoms moderately well, and September 9 the cataract in the left eye was extracted. Two weeks later it was found necessary to increase the dose of ephedrine to 50 mg. twice daily. He seemed improved and on October 3 a discision of the

left eye was done. Sixteen days later he had a recurrence of frequent Stokes-Adams attacks. The heart rate decreased to 12 per minute between attacks, and he became quite cyanotic and complained of sharp pain in the right arm. Large doses of caffeine-sodium-benzoate and epinephrine were given subcutaneously, but the patient died the next day during an attack.

Anatomical Findings.—The autopsy was performed thirty-six hours after death by Dr. T. T. Frost. We are indebted to him and to Dr. David Seecof for the pathological description of this case.

Heart: The heart weighed 550 gm. The epicardium in general was pale, smooth and glistening, except for two so-called "soldier's patches" measuring 2.5 by 3

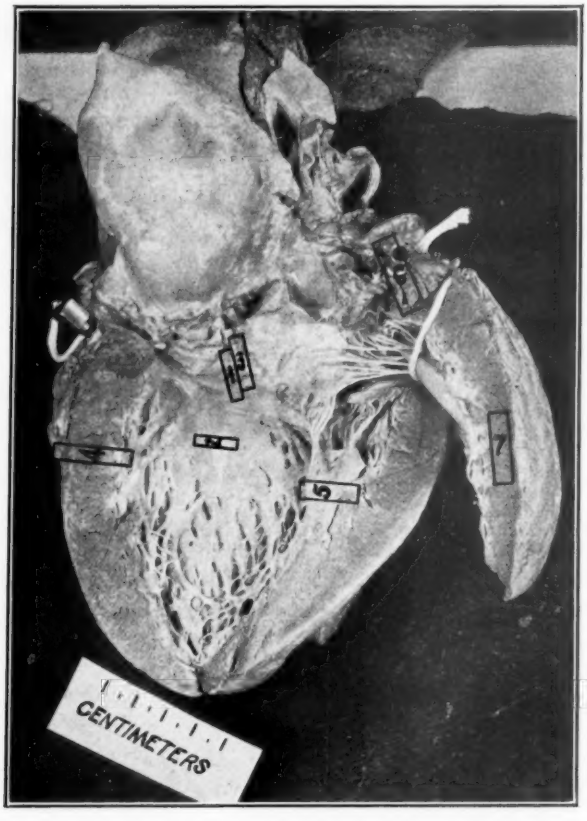

Fig. 2.—Left ventricle opened showing location of microscopic sections.

cm., one on the anterior and the other on the posterior surface of the right ventricle. The coronary arteries were straight and soft. On section, the myocardium was brownish red and no gross scarring was present. The right auricle was somewhat dilated and the pectinate muscles were hypertrophic. The endocardium was pale, smooth and glistening. The tricuspid leaflets and their chordae tendineae were not abnormal. The papillary muscles and trabeculae carneae were hypertrophied. The pulmonic leaflets were not abnormal. The left auricle was dilated, and the endocardium was slightly thickened and wrinkled. The mitral leaflets were irregularly thickened, particularly along the line of closure. At the base of the largest leaflet there was a thickened, irregular, calcified nodule, extending into the inter-

ventricular septum and through this to the base of the tricuspid leaflets. The chordae tendineae were slightly thickened but not fused or shortened. The papillary muscles and trabeculae carneae were somewhat hypertrophied. The endocardium of the interventricular septum showed several areas of opaque thickening. The pars membranosa of the interventricular septum was translucent and vascularized, and in the myocardium adjacent to it there was a small calcareous nodule 3 mm. in diameter.

The aortic leaflets were irregularly thickened and the free borders were rolled outward. There were numerous calcareous nodules present. The sinuses of Valsalva contain numerous elevated, firm nodular plaques. Surrounding the aortic ring were numerous yellow calcified plaques from 1 to 10 mm. in diameter. The orifice of the right coronary was slightly narrowed. The coronaries were patent and their intima was irregularly thickened by small yellow elevated plaques averaging 3 mm. in diameter.

Microscopic Sections: (See Fig. 2, for location of cut sections.)

Section 1. Interventricular septum adjacent to pars membranacea: The endocardium on the side of the left ventricle was moderately thickened by fibrous tissue and at the thinnest portion of the section there was marked thickening with numerous areas of calcification. The superficial layer of muscle was replaced by fibrous tissue, which extended to a slight degree between the adjacent muscle fibers. Midway between the two ventricular surfaces there was moderate replacement of muscle fibers by a dense, relatively acellular, connective tissue. In the endocardium on the side of the right ventricle there was a small area of fibrous thickening. The vessels in this region revealed a moderate thickening and hyalinization of all three coats, which was more pronounced in the medium-sized vessels. They were surrounded by an increased amount of fibrous tissue. The remaining portion of the section showed occasional small areas of interstitial fibrosis. The muscle fibers were of average size with well-preserved cross striation. The majority of the nuclei were small and found close together. An occasional large nucleus with square ends was seen. No Purkinje fibers were present in this section.

Section 2. Interventricular septum 4 cm. below aortic ring. The endocardium was moderately thickened by a loosely arranged, relatively acellular connective tissue, in which were large cells cut in cross-section. These showed a superficial resemblance to myocardial cells but were larger and contained a greater proportion of cytoplasm, the nuclei were small and irregular in shape and there was a tendency toward peripheral arrangement of the contracted fibrillae. The vessels and myocardium elsewhere in this section were similar to those in Section 1.

Section 3. Pars Membranacea adjacent to Section 1: There were marked subendothelial fibrosis and large areas of calcification, chiefly on the side of the left ventricle. This fibrosis extended deeply between the fibers of the myocardium. In many places the muscle fibers were small, palely stained and vacuolated. No Purkinje fibers were present in this section.

Section 4. Wall of left ventricle and left descending coronary artery: The epicardium and subepicardial fat showed no abnormalities. The intima of the coronary vessel was moderately thickened by fibrous change. The adventitia was thickened by hyalinized fibrous tissue. The myocardium contained numerous irregular areas in which the muscle cells had been replaced by dense connective tissue. The muscle fibers were large and had well-preserved striations and large nuclei, many of which had squared ends. Brown pigment granules were frequently present in the cytoplasm near the nuclei. The small coronary vessels showed a moderate degree of fibrosis. The endocardium was slightly thickened by acellular fibrous tissue.

Section 5. Posterior papillary muscle. There was a slight degree of acellular fibrosis throughout. The large coronary vessels showed marked thickening of the

intima by hyalinized connective tissue, and the adventitia was surrounded by an increased amount of dense, slightly cellular connective tissue. There was slight intimal fibrosis of the smallest vessels. The endocardium was moderately thickened by acellular fibrous tissue. The myocardium in this section was the same as in previous sections.

Section 6. Base of heart including left ventricle, left auricle, left circumflex artery and base of mitral valve: The intima of the coronary artery was considerably thickened by fibrous and hyalinized fibrous tissue. In the deep layers of the intima an occasional small capillary was present, and there was a slight infiltration of lymphocytes and an occasional polymorphonuclear leucocyte. The base of the mitral leaflet contained an increased amount of acellular hyalinized connective tissue. The endocardium of the left auricle was moderately thickened by acellular fibrous tissue. Myocardium was similar to that described above.

Section 7. Left ventricle taken parallel to surface and 3.5 cm. from apex: There is a slight degree of interstitial, acellular fibrosis, and moderate fibrosis of the small coronary vessels.

Note: No Aschoff bodies were present in the myocardium in any of the sections.

Aorta: The aorta measured 9.5 cm. in circumference at the arch. Extending throughout the aorta, particularly in the lower portion, there were yellowish gray, elevated plaques projecting above the cut surface. These were calcified in the region of the bifurcation. Microscopically there was marked intimal thickening by hyalinized connective tissue. The media showed a moderate degree of fibrosis. In the adventitia the vessels were slightly thickened and no cellular infiltration was present.

Femoral Artery: The vessel was markedly and irregularly thickened and calcified, particularly in the media. The size of the lumen was reduced by more than half. Microscopically there was extreme fibrosis and calcification of the media and marked irregular thickening of the intima by fibrous and hyalinized fibrous tissue.

Pathological changes of the other organs include a bilateral bronchopneumonia, pulmonary emphysema, arterial and arteriolar nephrosclerosis, and chronic cholecystitis with cholelithiasis.

DISCUSSION

This case of Stokes-Adams disease is one of the first reported as being successfully treated with ephedrine. In 1923 Feil[1] and other workers[4, 5] had reported the successful use of epinephrine in this disease, and because of the similarity of action of the two drugs we decided to try ephedrine in our case. In 1925 Miller[3] had reported the use of ephedrine in a patient having heart-block without Stokes-Adams attacks. The drug was used subcutaneously in 100 mg. doses, and there followed an increase in both auricular and ventricular rates as shown by electrocardiograms. In 1927 Hollingsworth[2] reported a case of Stokes-Adams disease which showed absence of attacks after receiving 50 mg. of ephedrine by mouth daily. Polygrams of the case were published but no electrocardiograms were taken. These two case reports were the only ones found in the literature. Recently, Wood[7] reported the use of the drug in Stokes-Adams attacks.

According to Karsner[8] the most common cause of permanent A-V block is coronary disease with its narrowing of the vessels supplying

the junctional tissues. As the vessels narrow, the A-V bundle and node undergo extensive degeneration and fibrosis. While our patient showed marked arteriosclerosis of his peripheral vessels both clinically and at autopsy, the coronary vessels were not seriously involved.

Looking for other explanations for the changes in the bundle, such as rheumatism, syphilis, diphtheria, scarlet fever or toxic agents, we find a lack of sufficient clinical and pathological evidence to ascribe the cause of the changes to them. We must then assume that the coronary sclerosis was sufficient to account for these changes.

SUMMARY

Subsequent observations with necropsy findings are recorded in a case of complete heart-block whose attacks of Stokes-Adams syndrome with periods of ventricular standstill were previously reported as having been controlled with ephedrine.

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CONGENITAL HEART-BLOCK

A Case With Other Cardiac Anomalies in a Student of Twenty-One Years*†

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ALTHOUGH heart-block is a grave omen, it does not of itself mean an early death. Taussig[1] has made the diagnosis in a woman of seventy-two years, whose pulse had been slow all her life, and who died of pneumonia four years later without signs of congestive failure. Hyman[2] has reported complete heart-block in an active, healthy man of fifty-eight years, whose pulse had been slow since the age of twelve years, "if not before." Pace[3] has recorded another asymptomatic case with bradycardia of thirty-four years' known duration. White[4] has under observation a woman, now forty-two years old and a champion golfer, with proved heart-block of fourteen years' standing. Death from heart failure in cases of block is due to failure of the myocardium.

Forty-four cases of congenital heart-block (complete in thirty-five) have just been reviewed by Yater, Lyon and McNabb.[5] In six cases the heart was apparently normal except for the dissociation. In the majority, however, the clinical diagnosis was patent interventricular septum, and this defect was present in the five that came to necropsy. The atrioventricular bundle studied microscopically in three was imperfectly developed. Three other clinical cases of complete heart-block have been reported, two by Ellis[6] and one by Wood and Roger.[7] Prenatal bradycardia was noted in only one of the forty-seven.

When heart-block is discovered after the age of twenty years, it is difficult to be sure that it antedated birth. Diphtheria is thought by some not to cause permanent block. If this be so, when a patient with heart-block who has never had rheumatic fever states that his slow pulse was first observed in youth, it is reasonable to assume that the dissociation is congenital; only a previous normal electrocardiogram can prove the contrary. Therefore the heart-block in the patients of Taussig, Hyman, Pace and White (aged seventy-six, fifty-eight, forty-eight and forty-two years respectively) was probably of congenital origin, and three of these authors inclined to this opinion.

REPORT OF CASE

In the course of routine examination of the students at the Georgia School of Technology, September, 1931, interest was attracted by the slow pulse and the cardiac murmur of B. H., a slender, fairly well developed boy of nineteen years. He

*From the Emory University School of Medicine.

†The patient was presented before the Fulton County Medical Society on April 20, 1933.

stated that his pulse had always been slow. A tentative diagnosis of congenital heart-block with patent interventricular septum was made.

Mr. H., the boy's father, said that he himself had always enjoyed good health and that he had not used alcohol before 1920; he was not related by blood to his wife. Mrs. H. had never been particularly strong, but she had given birth to a normal baby both before and after B. In the summer of 1911 she was ill with malaria. Since she failed to rally satisfactorily, a laparotomy for suspected ovarian disease was advised. Operation revealed early pregnancy but no pathological condition. Before she came to term some months later, the family doctor noted that the fetal heart was slower than the maternal. After delivery B.'s pulse was

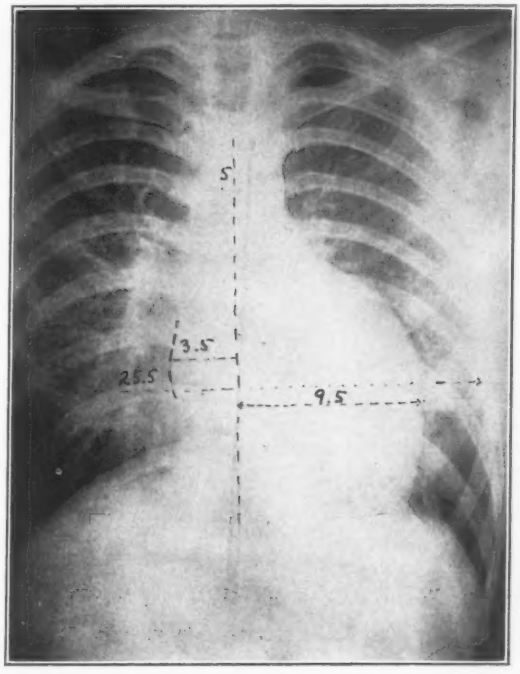

Fig. 1.—Anteroposterior teleroentgenogram. The silhouette suggests that of a guinea hen. It may be that torsion conceals hypertrophy of the right ventricle, which thus forms the apex. It may be that the hilar thickening is the result of hypertension in the pulmonary circulation. (Courtesy Dr. E. D. Shanks.)

still slower than his mother's. He was a blue baby. After a time the parents were told that he would "outgrow" his slow pulse, and they ceased to worry about it.

Except for repeated attacks of tonsillitis, B.'s childhood was essentially normal; cyanosis was not noted again and he experienced no dyspnea. Then frequent seizures of vertigo, and headaches with nausea and vomiting after unusual exertion began to annoy him. One hot day when he was nine years old, B. was sent to fetch a bucket of water and he fainted, remaining "limp for some ten minutes." A year later Dr. Albert E. Taussig reported, "The pulse was 44, rising only to 56 on violent exertion; the auricular rate was 109 as shown by the electrocardiogram, with complete auriculoventricular block." Though moderate restriction of activity was advised, the boy was encouraged to lead a normal life so far as the efficiency of his cardiovascular system would permit. The best criterion of this efficiency is

that B. fractured his left femur playing sandlot football in 1927. Headache and vomiting have recurred only once or twice since he first saw Dr. Taussig. He has never had any precordial pain or edema, but he has been taught to rest whenever tired.

Physical Examination.—There are no signs of edema, cyanosis or clubbing. Precordial bulging is marked: by actual measurement, the anteroposterior diameter of the left chest is from 1.5 to 2.0 cm. greater than that of the right. The apex beat is visible in the fifth interspace about 9 cm. from the midline, and retraction of the short ribs on the left synchronous with the heart beat can be seen behind. The left border of cardiac dullness extends 10 cm. in the fourth and fifth interspaces, and 7.5 cm. in the third. There is no increase in dullness to the right. A short, faint systolic murmur is heard at the apex and a long diastolic murmur to the left

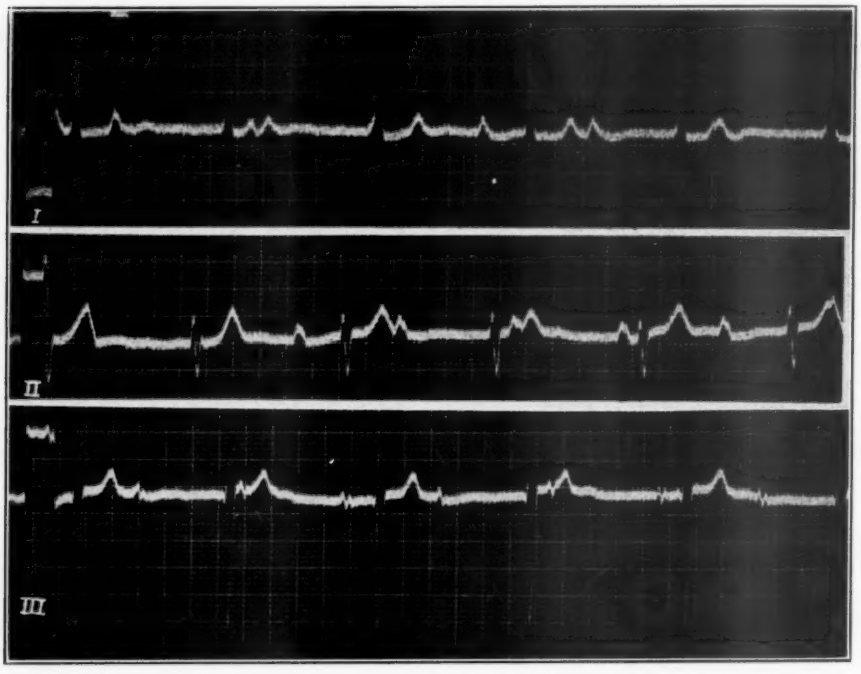

Fig. 2.—Electrocardiogram taken March 10, 1933. Auricular rate 66, ventricular rate 54: complete dissociation. (Courtesy Dr. E. D. Shanks.)

of the sternum, perhaps loudest about the third interspace, is present. The pulmonic second sound is accentuated: it is sharp and distinct several centimeters from midline. The pulse is of the "collapsing" type and there is a marked "pistol shot" in the groin. The pulse rate is 51 per minute. The systolic blood pressure is 110 mm.; there is a change in the character of the sound at 40, but it does not fade out until the mercury reaches 10 mm. Physical examination otherwise and routine laboratory tests are without interest. The anteroposterior teleroentgenogram is reproduced in Fig. 1; diagonal views with the esophagus visualized show that the left atrium is not enlarged, but indicate that the left ventricle is. One of the many electrocardiograms, all of which showed complete block, is shown in Fig. 2.

Epinephrin (0.5 c.c.) was administered. During the height of the reaction, which came after the electrocardiograph had been disconnected, 44 contractions (including four extrasystoles) to the half minute were heard at the apex.

DISCUSSION

The prenatal bradycardia, the immediate postnatal observations, the repeated records of slow pulse during infancy and childhood, the dramatic syncope at the age of nine years, the graphic evidence of heart-block at ten years, the absence of syphilis, diphtheria and rheumatic fever, all indicate that this heart-block is of congenital origin.

Although Abbott has emphasized that an accurate diagnosis of cardiac anomalies is often possible in an adult, a satisfactory one cannot be made in this case. Roentgenological studies often aid in the differential diagnosis, but they fail here because no similar one in a case that came to necropsy has been found. We believe that there is a lesion in the vital region of the membranous interventricular septum, which probably involves the right aortic leaflet, thus producing incompetence of the valve. This valve may be bicuspid. Intrinsic maldevelopment of the conduction bundle is almost certainly present.

Of greater clinical importance than the exact anatomical diagnosis, however, is the efficiency of the heart. Although this is hampered in B.'s case by the associated anomalies, which make strenuous forms of exercise inadvisable if not impossible, he has functionally a much better heart than ever had the noted musician reported by White and Sprague,[8] who died of a cerebral accident in his sixtieth year. It is therefore entirely possible that B. may round out a successful career in his chosen profession. He is fortunate in having the means to secure a good education and in having been able to become well adjusted to his limitations. He is more than fortunate in having first consulted a wise physician who did not limit his activities more than was necessary, nor precipitate a disabling cardiac neurosis. Now that he has passed through adolescence, I am satisfied that the danger of heart failure is remote.

SUMMARY

In cases of congenital heart-block the prognosis depends largely upon the extent to which the anomalies which are usually concomitant limit the functional capacity of the heart. If these permit the subject to survive the early years, his future depends principally upon the intelligence of himself and of his physician.

Complete heart-block of congenital origin with structural anomalies in the case of a college student, now twenty-one years old, is reported. Bradycardia was first noted before birth. Although his physical activities are moderately limited, he may live another fifty years. Early heart failure is not to be expected.

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Society Transactions

AMERICAN HEART ASSOCIATION, 1933

THE ninth annual scientific session of the American Heart Association was held at the Knickerbocker Hotel, Milwaukee, Wis., on June 13, 1933, with Dr. Walter W. Hamburger as presiding officer.

Program

Introduction. Walter W. Hamburger, M.D., Chicago, Ill.

Cytological Studies of Granulomata and Exudates From Patients With Rheumatic Fever. Currier McEwen, M.D., New York, N. Y.

ABSTRACT

Work previously reported has shown that rheumatic granulomata, as exemplified by the subcutaneous nodules, contain as their outstanding cytologic components, large cells having a characteristic appearance when exposed to neutral red and Janus green by the supravital technique. These cells differ in their reaction to these dyes from the characteristic cells of tuberculous and experimental syphilitic lesions. Essentially similar cells have been found in a further study of subcutaneous nodules from 7 patients with typical rheumatoid arthritis. They were not found, however, in examinations of 63 samples of joint exudate, 8 of pleural exudate, and 4 of pericardial exudate from 33 patients with rheumatic fever; or in 27 similar exudates from patients with other diseases. There was nothing characteristic in the joint exudates examined which served to differentiate those from patients with rheumatic fever. In the latter polymorphonuclear leucocytes predominated in most samples but tended to decrease in proportion to the clasmatocytes as the joints recovered. Clasmatocytes were also proportionately more numerous in exudates from patients over thirty years of age. From 3 to 20 per cent of lymphocytes and monocytes were present in most samples. The cells of pleural and pericardial exudates from patients with rheumatic fever were approximately the same as those of joint exudates save that 2 to 14 per cent of serosal cells were found in every sample.

The Importance of Allergy in Rheumatism. Edwin P. Jordan, M.D., Chicago, Ill.

ABSTRACT

There are numerous recent references to rheumatic fever as a manifestation of allergy. The evidence in favor of this hypothesis is based mainly on analogy, since the reproduction of rheumatic fever in experimental animals has not been successful. It was the purpose of the present work to determine whether joint lesions similar in character to those occurring in human joint disease and to those resulting from experimental allergic inflammation could be produced by nonprotein containing irritants. For this purpose turpentine and xylol were used. One c.c. of turpentine was injected directly into the right knee joint cavities of rabbits, and a similar amount of xylol into the opposite knee. The animals were sacrificed at varying periods of time following the injections and the synovia and the surrounding joint structures examined. In rheumatic fever in man the primary lesion of the joint appears to be synovial. In the experimental animals used the pathological changes

in the synovia can be traced through various acute stages to chronic or healing stages. From this work it appears that synovitis produced in rabbits by chemical irritants is not essentially different from that produced by the allergic inflammation observed by others. It is therefore not safe, in the present state of our knowledge, to draw etiological conclusions in rheumatic fever from the similarity of pathological changes produced in the joints of experimental animals by allergic inflammation.

Studies on the Etiology of Rheumatic Fever. T. Duckett Jones, M.D., and Josephine McBroom, A. B., Boston, Mass.

ABSTRACT

The etiology of rheumatic fever remains obscure despite much attention and extensive study of the disease during recent years. The evaluation of the rôle of the streptococcus, and more particularly of the hemolytic streptococcus, is discussed, especially in relation to throat culture work in rheumatic fever. Immunological reactions have not yet definitely proved any specific hemolytic streptococcus activity in rheumatic fever. Throat cultures have been made on 245 patients over a period of three and one-half years. The frequency of respiratory infection in this group is given, as well as the frequency with which hemolytic streptococci appear in the throat during the respiratory infection which precedes rheumatic fever. The close clinical relationship is noted. However, a close clinical relationship alone is not sufficient proof that the hemolytic streptococcus is the etiological agent in rheumatic fever.

Bacteriological Study of Throats in Rheumatic and Nonrheumatic Fever Cases With Special Reference to Hemolytic Streptococci. Israel Weinstein, M.D., and Norma C. Styron, A.M., New York, N. Y.

ABSTRACT

The investigation included 321 cases and 840 cultures taken from Montefiore and Bellevue Hospitals, New York City. Forty-six per cent of the cases were rheumatic fever patients. Fifty-eight per cent of the cultures were from this group. The remainder were from normal persons and those suffering from diseases other than rheumatic fever.

The results showed that hemolytic streptococci occurred no more frequently in the throats of rheumatic fever patients than they did in the throats of other individuals. During an upper respiratory infection the percentage of cultures showing hemolytic streptococci was no greater in the case of rheumatic fever patients than in other groups. However, young rheumatic fever patients suffering from an upper respiratory infection showed hemolytic streptococci in their throats more frequently than did older rheumatic patients. Those who had had their tonsils removed had these organisms less frequently associated with an upper respiratory infection than did those who retained their tonsils. In the groups studied, exacerbations of acute rheumatic fever occurred as frequently when there was no throat infection as when there was. The fact that the majority of those in whom exacerbations of rheumatic fever occurred were individuals having hemolytic streptococci in their throats suggests a possible relationship between this organism and the reappearance of the symptoms.

Dissociation of Streptococci Obtained From Acute Rheumatic Fever. Katharine M.Howell, M.D., and Eleanor P. Burton, A. B., Chicago, Ill.

ABSTRACT

Strains of streptococci were obtained by blood culture from four patients during acute attacks of rheumatic fever. On blood agar, two strains were anhemolytic, one

slightly hemolyzing, and one greening. The anhemolytic strains grew in broth with uniform turbidity, the others with granular sediment. According to Holman's classification, based on sugar fermentations, the anhemolytic strains were streptococcus salivarius, the hemolytic, streptococcus pyogenes, and the viridans, streptococcus mitis. Three of the strains were highly virulent for white mice, the fourth (an anhemolytic strain) moderately virulent. Search for dissociation in these freshly isolated strains began with the original cultures and continued for months under various conditions. The original colonies from each strain were small, round, smooth, pyramidal, entire, and metallic. Films from all cultures revealed diplococci and short chains; bacillary forms, swollen cocci, and bizarre forms frequently occurred. Many types of media, chemicals, anaerobic conditions, animal passage, ageing, etc., were employed to induce dissociation. Unfavorable environmental conditions produced SR forms—granular consistency, roughened wavy edges, granular projections, and daughter colonies. Microscopically, marked pleomorphism was observed. These were the only indications of dissociation. Subcultures reverted to smooth types. Conclusion—the four freshly isolated strains of streptococci obtained by blood culture from acute rheumatic fever remained virulent, smooth and stable for five months. Elements of dissociation in the strains are suggested by pleomorphism and by occasional SR colonies. Prolonged cultivation with loss of virulence may induce dissociation.

Rheumatic Manifestations in Subacute Bacterial Endocarditis in Children. Otto Saphir, M.D., and S. Wile, M.D., Chicago, Ill. See page 29.

A Clinical Conception of Rheumatic Heart Disease. Samuel A. Levine, M.D., Boston, Mass. See page 26.

Clinical and Pathological Study of One Hundred Cases of Mitral Disease. Charles S. Stone, M.D., and Harold Feil, M.D., Cleveland, Ohio. See page 53.

A Pathological Study of the Relationship of Auricular Fibrillation to Mitral Stenosis and Certain Rheumatic Tissue Changes. Clarence de la Chapelle, M.D., Irving Graef, M.D., and Antonio Rottino, M.D., New York, N. Y.

ABSTRACT

One hundred and eleven rheumatic hearts, obtained at necropsy in the past 13 years from the Third (N. Y. U.) Division of Bellevue Hospital, were examined. Forty-one were from patients who had established auricular fibrillation and 70 from patients who had sinus rhythm. The grade of stenosis was estimated as severe, moderate, or mild. Evidence of rheumatic inflammation was based on macroscopic examination in all and microscopic in 80. Blocks were taken after the method of Gross and Antopol. Of the 41 cases of fibrillation, 27 were over 40 years of age. Of the 70 cases of sinus rhythm, 28 were over 40. The grades of stenosis bore no relationship to the rhythm. Rheumatic inflammation was present in all cases of fibrillation under 40 years, and in only one-third of the cases over 40, independent of the grade of stenosis. This indicates that age may be a determining factor for the appearance of fibrillation in older subjects. In the sinus rhythm group, activity was present in 30 of the 42 cases under 40 years; and in 12 of the 28 cases over 40. Of the associated cardiac lesions, *tricuspid stenosis* occurred more frequently in the *fibrillation* group. Other lesions were uniformly distributed in both groups.

Paroxysmal Pulmonary Hemorrhages: The Syndrome in Young Adults With Mitral Stenosis. B. S. Oppenheimer, M.D., and Sidney P. Schwartz, M.D., New York, N. Y. See page 14.

Embolic Manifestations in Rheumatic Heart Disease. Soma Weiss, M.D., and David Davis, M.D., Boston, Mass. See page 45.

Electrocardiographic Findings in Experimental Pulmonary Embolism. John P. Anderson, M.D., Cleveland, Ohio.

ABSTRACT

An ante-mortem diagnosis of pulmonary embolism is comparatively rare while post-mortem diagnoses of this condition are comparatively common. There are three causes of emboli: (1) rheumatic hearts which develop intracardiac thrombi; (2) coronary thrombosis with mural thrombosis; (3) thrombosis or thrombophlebitis post-operative or otherwise in the peripheral venous circulation. One is sometimes at a loss to explain why a patient with rheumatic heart disease suddenly starts having more trouble than formerly or why the usual dosage of digitalis no longer seems to control the ventricular rate in cases with auricular fibrillation, or why patients suddenly develop acute attacks of pulmonary edema. Pulmonary embolism always has to be thought of in such cases. Similarly cases arise when a differential diagnosis has to be made between coronary thrombosis and pulmonary embolism, and two years ago a case arose which showed fairly characteristic electrocardiographic evidence of coronary thrombosis and that along with fever, leucocytosis, shock, reduced blood pressure, and a questionable friction rub made the diagnosis of coronary thrombosis seem fairly definite. At autopsy no evidence of coronary thrombosis was found and an extensive pulmonary thrombosis was apparently responsible for these signs. It was then decided to produce some pulmonary emboli experimentally and to observe the electrocardiographic changes produced. Several dogs were used and fairly consistent results obtained. These included tachycardia with disturbance of S-T segments with inverted T-waves. Coronary T-waves were encountered only once. The work will suggest a rather more rigid requirement for the electrocardiographic diagnosis of coronary thrombosis but whether the tracings are sufficiently differentiated to warrant electrocardiographic diagnoses of pulmonary embolism is uncertain. (Lantern slides showing serial electrocardiograms were demonstrated.)

The Heart in Rheumatic Fever and Rheumatoid (Infectious) Arthritis. Arthur M. Master, M.D., and Harry L. Jaffe, M.D., New York, N. Y.

ABSTRACT

This investigation continues a study* to distinguish between rheumatic fever and rheumatoid (infectious) arthritis. Daily electrocardiograms have now been taken on 63 patients suffering from acute rheumatic fever and on 46 patients with rheumatoid (infectious) arthritis. Evidence of myocardial damage was present in 100 per cent of the patients with rheumatic fever as evidenced by auricular fibrillation, auricular flutter, auriculo-ventricular conduction defect of more than 0.22 seconds, heart-block with dropped beats, RS-T changes, T-wave inversions in leads I and II. There were many abnormalities such as sino-auricular block, premature beats, nodal tachycardia, interference of sinus and A-V nodal rhythms. Not one of the 46 cases of rheumatoid (infectious) arthritis presented any of these abnormalities. In 5 cases the P-R interval reached 0.21 seconds, in one it measured 0.22 seconds. In 4 patients the T-waves were flat (iso-electric), once in lead I and thrice in lead III but not in a single instance was the T-wave inverted. In one patient there was a questionable reduction in voltage of the QRS group. Electrocardiographic evidence of myocardial involvement seems to be of real value in distinguishing rheumatic fever and acute rheumatoid (infectious) arthritis.

*Rheumatoid (Infectious) Arthritis and Acute Rheumatic Fever. J. A. M. A. 98: 881, 1932.

Lesions of the Kidney Associated With Rheumatic Heart Disease. Ann Purdy, M.D., San Francisco, Cal.

ABSTRACT

This article reviews briefly the literature in which kidney disease has been reported as occurring in the course of rheumatic heart disease. The author adds 2 cases of her own of hematuria in acute rheumatic fever in which the urine sediment did not return to normal in convalescence. No case is reported in which the kidney findings did not antedate salicylate therapy. This is followed by a survey of the heart and kidney findings in a selected group of cases seen in 3 cardiac clinics in San Francisco where rheumatic fever is said to be modified by climate. The cases were not selected alphabetically or chronologically; the families with "leads" were surveyed first. The cross-section of the group is in process. Some of these cases are pedigreed rheumatics, some are early and the diagnosis is open to question. All were studied in their family groups. A group of tonsillitis cases is reported. This group has been retained in the cardiac clinics by reason of their having been seen in an acute tonsillitis, or its allied diseases, or because they give a convincing history of them. They are being periodically scrutinized for the alleged sequelae. The pathological findings in the kidneys of patients dying of rheumatic heart disease and the pathological findings in the hearts of patients dying of nephritis are given. The clinical data are put forward for what they are worth, claiming not completeness, but timeliness. This article does not concern itself with the bacteriological considerations of these diseases and makes no etiological claims.

Skin Lesions in Rheumatic Fever: Observations on the Predominating Signs of Active Rheumatic Fever During a Ward Epidemic. William Chester, M. D., and Sidney P. Schwartz, M.D., New York, N. Y.

ABSTRACT

Skin manifestations have not received the attention they deserve as signs of activity in rheumatic fever. In a ward epidemic of this disease observed at the Montefiore Hospital during the months of March to November, 1931, 10 of 21 children showed skin lesions as the predominating sign of a recurrence or exacerbation of rheumatic fever. These lesions were most prevalent during August and September of that year and they occurred in crops. They appeared mainly on the lateral surface of the legs and the extensor surface of the forearms. They were rarely seen on the anterior trunk of the body. The regions about the joints were seldom involved. Their color was bluish, they were not tender, and varied in size from a lemon seed to a hazelnut. Most often they appeared as maculo-papular purpuric spots and persisted for from 1 to 6 months. In fading away very gradually, they underwent the pigmentary changes seen in subcutaneous hemorrhages with extravassation. No scarring or desquamation was seen to follow their disappearance. A total of 22 crops of skin lesions were studied in these 10 children. In 19 instances, an increased heart rate was an accompanying sign. Fever was present in a mild form on 13 occasions. Joint and muscle pains, choreiform movements, epistaxis, and congestive heart failure were each present in 2 instances. Hematological studies showed a persistent secondary anemia in all cases, a leucopenia and a positive Shilling count in 2 cases, and a transient thrombocytopenia and a positive tourniquet test in only one case. In one instance the P-R interval was prolonged. The appearance of skin lesions in children who have already had rheumatic fever should be considered as much a sign of reactivity as any other criterion accepted to date.

Incidence and Clinical Notes of Rheumatic Heart Disease in Southern Florida. E. Sterling Nichol, M.D., Miami, Fla. See page 63.

Convalescent Care of Cardiac Children. Hugh McCulloch, M. D., St. Louis, Mo.

ABSTRACT

When the course of rheumatic heart disease shows progressive improvement, the management of the patient must be adjusted to the changed conditions, so that further improvement is favored and any relapse is prevented. This management is always to be adjusted to the individual circumstances and only general indications can be discussed. Progress will be determined by: (1) the type of response shown by the patient during the attack of rheumatic fever and heart disease; (2) the severity of the cardiac injury; (3) the number of preceding attacks; (4) the age of the patient. Useful signs of progress are: gain in weight, steady heart rate and body temperature, and physical signs in the heart of improvement. Influence of seasonal tendency to recurrence. Discussion of institutional convalescent care and relationship of cardiac child to school.

The Course and Prognosis of Rheumatic Fever and Chorea. T. Duckett Jones, M.D., and Edward F. Bland, M.D., Boston, Mass.

ABSTRACT

The House of the Good Samaritan, Boston, Massachusetts, has since 1921 devoted a large number of beds to the hospital care of patients with rheumatic fever and chorea. In 1930 with the organization of a Research Department, an attempt was begun to assemble complete records and careful follow-up studies on these patients. With the cooperation of the large general hospitals of Boston and the institution of 2 weekly Out-Patient Clinics at the House of the Good Samaritan, a large amount of data has been assembled. A group of 1000 consecutive cases has been analyzed in an attempt properly to evaluate the life cycle of rheumatic fever and the resultant heart disease. The brief analysis here presented concerns itself largely with the frequency of the signs and symptoms of the disease, the frequency of reinfections, the importance of respiratory infections in connection with the disease, the seasonal and annual incidence, and prognosis.

Discussion

Discussion of paper by Dr. McEwen.

Dr. Arthur M. Master, New York, N. Y.—Are the refractive bodies in the cells or in the granules seen in the neutral red stain different in the subcutaneous nodule of rheumatic fever and rheumatoid (infectious) arthritis?

Dr. McEwen.—In the nodules studied there tended to be more of the spindle-shaped cells in those from patients with rheumatoid arthritis, and such nodules not infrequently contained cells showing refractive bodies of larger size than any seen in cells from rheumatic nodules.

The majority of cells, however, were essentially the same so that one would have been unable to say, from examinations of individual cells, which type of lesion they came from. None of the characteristic cells from either type of nodule contained bodies which stained with neutral red.

Discussion of paper by Dr. Jordan.

Dr. A. G. Young, Boston, Mass.—Dr. Jordan's paper and the microscopic sections he has just shown do not convince me that he has ruled out the possibility of an allergic reaction in rheumatism. His slides show the usual inflammatory reaction to a chemical irritant. This does not coincide with the findings made by Dr. McMahon and myself in tissues taken from rheumatic fever and infectious arthritis patients. In the early acute stage one finds a flaky fluid exudate in the joint cavity containing few cells whereas the periarticular tissue is the seat of an acute inflam-

matory edema. The membrane is swollen, thickened and covered with a delicate fibrinous coating. The villi are thickened and the capillaries are markedly affected. Microscopically one finds synovial cells forming a thickened somewhat palisade-like wall. There are minute foci of necrosis, bordered by degenerating cells. The villi are enlarged, the connective tissue is edematous and infiltrated with few polymorphonuclear leucocytes and lymphocytes. In the deeper surrounding connective tissue Aschoff bodies may be found. I realize the difficulty in showing the entire pathological picture by lantern slides, but from what I have seen and from what Dr. Jordan has described I cannot agree that he has reproduced the rheumatic fever type of joint reaction by his chemical irritants.

Dr. M. H. Dawson, New York, N. Y.—It is very interesting to learn that Dr. Jordan has been able to reproduce with nonprotein substances the same type of lesion which Klinge produced by serum injections in sensitized animals. However, there is a doubt in my mind as to whether the lesions produced by Klinge and by Dr. Jordan are the same as those which occur in rheumatic fever and rheumatoid arthritis. The type of reaction in the naturally occurring diseases possesses certain rather distinctive characteristics which I do not believe have as yet been produced experimentally.

Dr. Jordan.—I hope that I have made clear that these findings are not an argument against allergy as the cause of rheumatic fever. The fact that a chemical irritant can produce pathological changes so similar to human arthritis is, however, an indication that great conservatism should be used in arguing by analogy. The palisading which Dr. Young mentioned does not seem to be a characteristic feature either of human synovia in arthritis or of the chemical synovitis.

Discussion of paper by Drs. Jones and McBroom.

Dr. Jones.—All students of rheumatic fever heartily agree that the disease is a general one, and the concentration of attention on respiratory infection and throat cultures does not in any way indicate that I am unaware of this important feature. The careful study of a large control series would be very valuable. The frequency with which hemolytic streptococci are present in the throat in normal persons during respiratory infection has not been sufficiently well observed. It may be well to stress the fact that recurrences of rheumatic fever occur in the absence of preceding respiratory infection, and that recurrences may help us to evaluate possible etiological agents.

Discussion of paper by Drs. Howell and Burton.

Dr. M. H. Dawson, New York, N. Y.—In a recent study of bacterial dissociation of *Streptococcus hemolyticus* we have been able to obtain quite similar types of colony variants. In our experience there is always a close relationship between colonial morphology and the morphology of the individual organisms constituting the colony.

Discussion of paper by Drs. Saphir and Wile.

Dr. Wm. Thalhimer, Chicago, Ill.—In spite of the diversity of opinion about rheumatic fever there is one point on which all investigators will agree; the cause of this disease has not been unquestionably established. Studies of rheumatic fever in recent years have concerned themselves chiefly with two subjects: The origin, nature and significance of Aschoff bodies—and the possible etiological relationship of streptococci to this disease. Thayer, in one of the last articles he published, stated that "streptococci have not been proved to be the cause of rheumatic fever." No new or conclusive evidence has been brought forward since Thayer's article.

The conception of the streptococcal cause of this disease, as a matter of fact, is not new, dating back to Poynton and Paine, and even earlier. The ease with which these workers recovered streptococci in blood cultures (in one instance by culturing two drops of blood from the ear into a flask of broth) is in striking contrast to the difficulty more recent workers have had. Poynton and Paine also believed, as some still do today, that subacute bacterial endocarditis is a malignant form of rheumatic fever.

At present there are two schools. One believes that streptococci are the direct cause of the disease and of the pathological changes found. The other believes that the same, or similar streptococci first cause an allergic condition and later stimulate repeated allergic responses which constitute the disease rheumatic fever.

The first group have recovered slow growing green or indifferent streptococci from the blood of about 60 to 70 per cent of the febrile patients studied, and these positive blood culture results decreased rapidly with the decrease and disappearance of fever. Nevertheless, the control group of blood cultures were taken on afebrile patients with other diseases. Surely a control group must be chosen as carefully as the experimental group, and one worker has secured streptococci in a large percentage of blood cultures from febrile, non-rheumatic patients.*

It is not my purpose to give the impression that cultivating these streptococci is a simple, easy job. It requires infinite care and excellent bacteriological technic. But Reith and Squier,† with a similar technic have recovered streptococci from a not insignificant number of apparently healthy individuals, who were well enough to carry on hard manual work.

Today, the recovery of an organism from the blood of a patient is not sufficient evidence that this is the cause of the patient's disease. Other criteria must be satisfied, even more today than when Koch announced his postulates. If streptococci cause rheumatic fever, we would expect to find them in appreciable numbers in the acutely and severely damaged heart valves and myocardium in this disease. I have never been able to find them at all, and cannot believe that an occasional coccus or diplococcus found, and then only after most careful and extensive search, can have any real significance. In other mortal, and less mortal, streptococcal diseases there is no difficulty in demonstrating streptococci in large numbers in the lesions.

Those who propose the streptococcus allergic theory as the cause of rheumatic fever cannot be right if streptococci are present in the blood stream of these patients, since they have shown experimentally that streptococci introduced into the blood stream destroy the previously developed allergic condition. Also, they have not been able to terminate the allergic state in human beings; i.e., the disease, by the intravenous injections of streptococcus vaccines. They believe that rheumatic fever develops at times into subacute bacterial endocarditis and with this the allergic state changes to a condition of immunity. Since individuals with this last disease almost invariably die, they can only be considered immune in a sense different from the usually understood meaning of immunity. Also, the presence of agglutinins in the blood does not indicate immunity (resistance to disease) any more than does the presence of complement-fixing bodies. The allergic theorists claim that they have produced Aschoff bodies in animals by means of repeated shocks caused by streptococci. This is doubted by some of us and brings up the dangerous question of the specificity and origin of these peculiar and interesting human lesions.

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*Since this discussion was presented an important article has appeared. May G. Wilson and Helen Edmond in the American Journal of Diseases of Children, page 1237, June, 1933, report the recovery of the same types of streptococci from blood cultures from children with rheumatic fever and from a control group either apparently normal or with non-rheumatic types of disease, the percentage of positive streptococcus blood cultures being about the same in each group.

†J. Infect. Dis. 51: 336-343, 1932.

I do not believe that these problems can be solved with our present knowledge and background. New methods or new material, or both, will be necessary. Some of us believe that Aschoff bodies have peculiar characteristics (which can be described and demonstrated) different from any experimental lesions which have been produced. Others believe the contrary and neither can be convinced of the opposite point of view. Manifestly, no progress can be made under these conditions.

The question of the specificity of Aschoff bodies for rheumatic fever is in the same situation. Since it is well known that attacks of rheumatic carditis can occur without any of the recognized signs of rheumatic fever, and therefore these attacks can even be subclinical and not recognized—the mere absence of a history of rheumatic fever does not prove that this disease did not afflict the patient. The association of Aschoff bodies with gross cardiac lesions recognized as those of rheumatic fever outweighs, in my opinion, the arguments for the non-specificity of these bodies.

The gross endocardial and cardiac lesions of rheumatic fever are so different from those of subacute bacterial endocarditis that it is difficult to believe that these two diseases can be causally related. Even if one believes that some of the microscopic endocardial lesions of the two "conditions" are similar, it seems to me that more than a similarity of inflammatory reactions is necessary to prove the same etiology for the two diseases. One illustration is sufficient; many causes of encephalitis are recognized, but the encephalitic lesions caused by the different agents are so similar that one cannot determine cause from examination of the lesions.

The nature of the onset of rheumatic fever, the recurrences, the holding on and never letting go of the disease rheumatic fever, the peculiar and characteristic nature of the gross and microscopic cardiac lesions, make me think that this disease is not bacterial in origin but that its causative agent is more likely to be virus or protozoal in nature. This conception is not new but it seems to me is worth reviving. Others have searched for a protozoan or virus cause of rheumatic fever without success and I also have made unsuccessful searches for unknown organisms in cardiac material from rheumatic fever. This is a difficult search but it still interests me and perhaps may interest some of you.

Dr. Emanuel Libman, New York, N. Y.—To my mind, Dr. Thalheimer has not chosen well in drawing a comparison between the non-hemolytic streptococci found in cases of rheumatic fever and the bacillus typhi-exanthematici, in connection with drawing conclusions as to the etiological significance of the streptococci. It is well known that there is much risk in drawing inferences from comparisons of the biological character of organisms and the immunological responses to them. In this particular instance the risk is much greater. The streptococci that have been found in the cases of rheumatic fever are also present in the blood of a great variety of other conditions. The bacillus typhi-exanthematici (a pure anaerobe) has been isolated only in cases of typhus fever. Similarly, complement-fixation reactions with this organism have never been demonstrated in the blood of any other diseases, whereas complement fixation against non-hemolytic streptococci is found in many other conditions and in rheumatic fever. Of interest also is the fact that the above mentioned bacillus was found by Olitsky in abundance in the intestinal contents of infected lice. That the organism has a definite relationship to the disease is evident, but its exact rôle is as yet undetermined. Much more could be added in this connection, but I have stated enough to indicate that the comparison which has been made is not of any definite aid to us.

I have not made this statement because I am convinced of the etiological significance of streptococci in rheumatic fever. On the other hand, I have always felt that there is no binding evidence of such a relationship. Many years ago, like some others, I pointed out that the etiological agent might not be one of the ordinary

bacteria—and perhaps not be in the bacterial group at all. It would take up too much time to discuss this subject fully. I have elsewhere taken it up and have shown that the non-hemolytic streptococci are ubiquitous and may invade the blood in practically any disease.

It has long been known that subacute bacterial endocarditis occurs mainly on the basis of valvular defects of rheumatic origin, commonly in congenital defects, much less often in connection with luetic or atherosclerotic lesions, and that occasionally an apparently normal valve is affected. Notwithstanding the great frequency of the infection in valvular defects of rheumatic origin there is no evidence that the two diseases have a similar etiology. Like Drs. Saphir and Wile, I believe that other factors, particularly of a mechanical kind, play a decisive rôle.

I long ago noted combinations of active subacute bacterial endocarditis and recent rheumatic infection. Fresh Aschoff bodies were found in cases of active subacute bacterial endocarditis, and they were also encountered in the myocardium in cases of old valvular defect in which histological examination showed only old fibrous and calcareous changes and no evidence of active rheumatic infection. Fresh Aschoff bodies may even be found in combination with subacute bacterial endocarditis in the bacteria-free stage.

In this connection the paper of Drs. Saphir and Wile is a striking contribution. As they say, these observations must be taken cognizance of, in connection with any immunological conceptions concerning rheumatic fever.

Not only may recent Aschoff bodies be found in cases of active subacute bacterial endocarditis, but even active rheumatic valvular involvement. Thus I have reported a case in which there were present active rheumatic endocarditis of the aortic cusps and the posterior mitral flap, and recent subacute bacterial endocarditis of the anterior flap. I have also observed the following combination: recent rheumatic endocarditis of the aortic cusps, subacute bacterial endocarditis of both mitral flaps, and recent rheumatic endocarditis of the left auricle, on top of part of which was implanted a fresh attack of subacute bacterial endocarditis.

In regard to the rôle of focal infections, especially tonsillar infection, some clarity may perhaps be obtained by reference to a hypothesis which I have been recently formulating. According to it—in brief—any toxic focus may cause hyperemia and edema in various tissues of the body, and particularly in those previously affected by any infection (or intoxication), or metabolic disturbance. According to this idea, an infected tonsil, for example, can cause an activation of joints previously affected by the rheumatic virus. It is perhaps in this way that we can explain at least some of the beneficial results as regards articular involvement, that have been attributed to tonsillectomy. It is also permissible to consider that a previously diseased valve (or even a normal one) may repeatedly react to toxic foci by hyperemia and swelling. In that way recurrences might be set up, and fibrosis eventually increased. Every attempt must be made to eradicate all toxic foci, apart from a consideration of their harboring the actual rheumatic agent.

There is evidence that valves may become the seat of acute or subacute bacterial endocarditis in more than one way. It is difficult to say definitely which comes into play more often, embolism of the valve or implantation from the general blood stream. It is not easy to conceive that the infection is brought about by separate organisms floating in the blood. Perhaps the studies of Bull may be applicable here. He found that when bacteria are injected into the circulation, agglutination precedes their destruction.

Dr. Arthur M. Master, New York, N. Y.—In a discussion of the time relation between the appearance of subacute bacterial endocarditis and the preceding attack of rheumatic fever there are cases in which subacute bacterial endocarditis suddenly appears during the course of an attack of acute rheumatic fever. A boy of 14 years and a young adult of 21 both were admitted to the hospital suffering from

active rheumatic fever with an acute polyarthritis; no petechiae were present, urine and blood cultures were negative. With the development of an aortic diastolic murmur a subacute bacterial endocarditis became evident,—petechiae appeared, red blood cells were found in the urine, splenic infarcts were noted, blood cultures were positive. Both patients died and the diagnosis of subacute bacterial endocarditis engrafted upon previous rheumatic lesions was substantiated in each case.

Dr. Currier McEwen, New York, N. Y.—It does not seem to me that the presence of Aschoff bodies in the hearts of children dying of bacterial endocarditis is sufficient, in itself, to disprove the theory that rheumatic lesions are produced in tissues hypersensitive to streptococci while those of bacterial endocarditis occur only in the presence of circulating antibodies; because in rabbits rendered hypersensitive to streptococci, circulating antibodies against the same microörganisms can be quite regularly demonstrated. It may still be true that, while the typical rheumatic response is based upon hypersensitivity and the typical lesions of bacterial endocarditis are associated with circulating antibodies, patients in transition from one state to the other may show lesions of both types. Of course, too, it is doubtful whether one can tell the age of Aschoff bodies in a given instance, so that when found in hearts of children dying of bacterial endocarditis, such Aschoff bodies may be merely evidence of recent rheumatic carditis.

Dr. Samuel A. Levine, Boston, Mass.—The finding of simultaneous evidence of rheumatic heart disease and subacute bacterial endocarditis in these cases does not militate entirely against the conception that there is some antagonism between the two states in adults. I believe that there is sufficient clinical evidence from a large series of cases of subacute bacterial endocarditis observed in adults to warrant the general conception that certain types of rheumatic heart disease are more and others are less likely to develop subacute bacterial endocarditis. It is rarely seen in patients who have had previous congestive failure or who have had auricular fibrillation. It occurs most commonly in those who are in fairly good health and who are comparatively free from rheumatism.

Dr. T. Duckett Jones, Boston, Mass.—I should like to call Dr. Wile's attention to the ideas of Dr. Ronald T. Grant of London, England. In a recent series of lectures on "The Pathology of Endocarditis" delivered in this country, Dr. Grant stressed the probable rôle of platelet thrombi on valve surfaces as offering a good nidus of growth for bacteria, and a logical forerunner of bacterial endocarditis. Should thrombi be present and not too well organized, a transient blood stream infection would be all that is necessary for the development of bacterial endocarditis. Experimental proof of this may be forthcoming. It offers a logical explanation for many clinical and pathological features.

Dr. Saphir.—In answer to the remark that allergy is a biologic phenomenon, very intricate and difficult to understand, and that it should not be ruled out too soon as the underlying factor of rheumatic fever, I should like to say that just because it is so intangible it should not too readily be used as an explanation of a disease such as rheumatic fever. We must maintain that at the present time the cause of rheumatic fever is not known. On the other hand, we do believe that the Aschoff body is a specific granuloma caused by the unknown virus of rheumatic fever. Nodules have been produced experimentally which some observers hold identical to Aschoff bodies. We must emphasize, however, that none of the published illustrations are typical of Aschoff bodies. Since we believe that Aschoff bodies have not been produced experimentally, we have no right to assume that we know the etiology of rheumatic fever. It might very well be that our findings substantiate Dr. Libman's theory that a streptococcus bacteremia may lower the resistance of

patients who have had a quiescent rheumatic infection, reactivate the rheumatic infection and hence explain the finding of recent Aschoff bodies in cases of subacute bacterial endocarditis.

Discussion of paper by Dr. Levine.

Dr. L. Lichtwitz, New York, N. Y.—The relationship of the endocrine make-up, i.e., the constitution, to rheumatic fever was recognized by the older generation of physicians, and is occasionally taken up in recent publications. The study of this question, however, has been almost entirely crowded out by the concentration of investigative work on the infectious side of the disease.

A mere reference to the incidence of chorea and of nodose rheumatism in the female sex, indicates the importance of the subject. But even apart from this easily recognizable endocrine relationship, there is a close connection between constitution and rheumatic fever, one of the striking facts being that the kind of rheumatic infection from which a person suffers is determined by the constitution.

From a broad clinical point of view, there are two kinds of rheumatic fever. The first is characterized by marked articular swellings, frequent cardiac involvement, rheumatic cutaneous changes, and alterations of the walls of the capillaries. There is but little tendency for the joints to become stiff, and anti-rheumatic medication has a marked influence. In the second type there is absence of joint swelling but a great tendency to stiffness, and absence of cardiac and cutaneous changes. This kind of rheumatic fever is resistant to anti-rheumatics. The first form is encountered in young people with a thyroidal constitution, and the second, in individuals of pyknic constitution.

Now the place of attack of every anti-rheumatic (analgesic, anti-pyretic) is the midbrain. It is certain that the hyperpyrexial form of rheumatic fever is a cerebral condition, with especial evidences of affection of the midbrain. The sweating of rheumatic fever, that occurs independently of use of medication, also signifies an involvement of the midbrain, just as oily skin and sweating do in epidemic encephalitis.

The midbrain is the most important regulator of every vegetative function—it is the most reactive and vulnerable part of the whole body. Fever and other phenomena of infection are evidences of this reactivity. Fever is significant of a regulating and defensive mechanism of the whole organism, just as local allergic or inflammatory phenomena are for a part of it.

We have been influencing the relationship and dependence of allergic reactions (of different kinds and degrees) to the midbrain and the neuroendocrine pattern—a question which is also of therapeutic importance.

Dr. B. S. Oppenheimer, New York, N. Y.—We have noticed a more than accidental association of rheumatic endocarditis, and also choreiform movements, and Graves' disease. The choreiform movements were much more marked than the gross muscular tremor or the exaggerated skeletal muscular movements which are observed at times in active Graves' disease. There appears to be some relation between Graves' disease, which manifests symptoms of endocrine disturbance, and the rheumatic group. The mechanism is not clearly established, but experience with instances of neurogenic Graves' disease has directed our attention to the sympathetic centers in the brain, and suggests that the common factor in the choreiform manifestations and Graves' disease may be found in the diencephalic centers which have just been discussed by Dr. Lichtwitz.

Dr. Emanuel Libman, New York, N. Y.—The subject introduced by Dr. Levine is surely one of real importance and interest. Some years ago I drew attention to

the apparent relationship of rheumatic fever and so-called status lymphaticus. A point worth following up is an apparent tendency for the occurrence of warts on the back of large flat hands of certain male adolescents having or developing aortic insufficiency.

Some years ago a rather elaborate paper was published in the *Wiener Archiv für klinische Medizin*, by Hammerschlag, dealing with the constitutional disposition to rheumatic fever. It is worthy of study for its suggestive content.

Discussion of papers by Drs. Stone and Feil; Drs. de La Chapelle, Graef and Rottino; and Drs. Oppenheimer and Schwartz.

Dr. Louis F. Bishop, Jr., New York, N. Y.—I should like to know the frequency with which hypertension was associated with mitral stenosis in the series of cases reported by Drs. Stone and Feil.

Dr. Emanuel Libman, New York, N. Y.—Hemoptysis in connection with cardiac disease needs much further study. Even a comparatively short study of the subject will make it clear that other factors apart from those of a mechanical nature must often play a rôle. In the course of a paper published in 1918 I went into this aspect of the subject. In four-fifths of cases of suspected infarction, for example, only pulmonary apoplexy was found at the post-mortem examination. I drew attention to the importance of studying any tendency to bleed in the patient, and showed that this tendency is greater in the presence of hepatic insufficiency due to tricuspid disease.

Duroziez in 1878 pointed out that epistaxis and hemoptysis may be part of rheumatic fever in itself. In 1875 he drew attention to hemoptysis in cardiac cases as a cause of menstrual irregularity. Peter made similar observations.

Of particular interest in the cases reported by Drs. Oppenheimer and Schwartz are the remarkable early symptoms of the attacks. It would be important to know whether they appeared in the first as well as in later attacks. If they appeared for the first time in later attacks they might be attributed to fright and fear. But if they occur in first attacks, we have here a clinical picture that, as far as I know, has hitherto not been reported.

Dr. Arthur M. Master, New York, N. Y.—The present authors and many others have recently given evidence that with good care a patient with severe rheumatic valvular disease will go through with pregnancy and labor. This good care usually consists of rest, rest in bed and avoidance of upper respiratory infection. However, although the cooperation between obstetrician and clinician will bring about these fine results it must not be forgotten that there may be a decided after effect on the mother. It is my impression that the more pregnancies the patient goes through the shorter is her life span. A clinical impression is not a scientific method, however, and we are gathering statistics on this subject. Definite conclusions can only be based on a larger series of cases than has been reported.

Dr. Oppenheimer.—I am obliged to Dr. Libman for calling attention to the work of Duroziez on hemoptysis and epistaxis. In our paper, it was not attempted to discuss the whole question of hemoptysis, which of course occurs in a great variety of conditions. There is as yet no consensus of opinion as to the mechanism of hemoptysis in these various pathological conditions; for example, the cause of bleeding in so-called essential hemoptysis and also in essential hypertension is not at all clear. We are calling attention to an exceptional group of cases of prolonged severe hemoptysis associated with mitral stenosis, with unusual psychogenetic symptoms. It will be necessary to look into the individual histories to see, as Dr. Libman has

suggested, whether the psychoneurotic symptoms occurred with the very first attack of hemoptysis, or whether the initial hemoptysis started an anxiety neurosis which accounted for the nervous symptoms which initiated or preceded subsequent attacks of bleeding.

Dr. Feil.—Our cases of mitral stenosis associated with pregnancy are too few in number to draw any sweeping conclusions concerning the effect of pregnancy on the duration of life. We do believe that pregnancy is well tolerated by the majority of patients with mitral stenosis.

Discussion of paper by Doctors Weiss and Davis.

Dr. Lewis A. Conner, New York, N. Y.—In connection with this interesting study of the embolic phenomena in rheumatic heart disease it is well to emphasize the need for prompt diagnosis and prompt operation in cases of embolism of the large arteries of the extremities and possibly also of the pulmonary artery and the mesenteric arteries. The saving of a limb or a life will often depend upon the degree of coordination existing between the physician and the surgeon and the promptness with which the operation of embolectomy is performed.

It is well known that the operation offers the best chance of success if done during the period of blanching which immediately follows the blocking of the artery and often lasts but a few hours. When time has been given for the formation of a thrombus distal to the embolus, the outlook is much less favorable. In cases of mitral stenosis with auricular fibrillation, which is the condition most likely to be associated with such large arterial emboli, this possibility should therefore be kept constantly in mind and everything possible done in advance to insure prompt action if that should become necessary.

Dr. Fred M. Smith, Iowa City, Iowa.—I should like to ask Dr. Weiss if he has observed any relationship between infection and embolic phenomena. In some of the cases that we have observed, embolic manifestations seemed to follow a recurrence of rheumatic infection.

Dr. James A. Lyon, Washington, D. C.—I have listened with much interest to Doctor Weiss's analysis of the group of autopsied cases having rheumatic heart disease with embolic occlusion. Recently in private practice I have seen two interesting cases of embolic occlusion of major arteries of the greater circulation, followed by coronary occlusion and death. An embolectomy was performed in each of the two cases.

The first case was that of a white man, twenty-eight years of age, a bank clerk by occupation, who had been under my observation for three years because of rheumatic heart disease, mitral regurgitation and stenosis, congestive failure, and chronic auricular fibrillation. While at work, the patient had a sudden attack of intense pain in both groins, causing him to fall suddenly to the floor in a state of collapse. A physician who was called diagnosed the attack as neuritis and arterial spasm. On the seventh day after this circulatory accident, the patient was seen by Dr. Philip O. Pelland, an orthopedic surgeon, who found an entire absence of circulation in both legs. The patient was then admitted to Garfield Hospital where I saw him in consultation. It was evident that the initial attack had been caused by a saddle thrombus at the bifurcation of the abdominal aorta, which later on became dislodged and divided, entering the common iliac arteries. The following day, eight days after the initial attack, an embolectomy was performed by Dr. Harry Kerr, staff surgeon. Circulation was re-established in both legs. Unfortunately, on the day following the operation and again a week later there were evidences of fresh arterial occlusions,

and both legs again became cyanosed and the femoral arteries pulseless. A second embolectomy was performed by Doctor Kerr. A clot seven centimeters in length was successfully removed from the right femoral artery, reestablishing the circulation, but the attempted removal of the clots from the left femoral was unsuccessful. The patient continued to have repeated embolic deposits in both femorals, and twenty-five days after the initial attack both legs were amputated above the knees. One week following the amputation, the patient suddenly died of coronary thrombosis. At autopsy the orifice of the right coronary artery was found completely occluded by a large thrombus.

In the second case the patient, a retired white man seventy-five years of age, had arteriosclerotic heart disease and angina pectoris, which had shown increasing severity for the past two years. He was under my observation for more than a year. His initial attack was accompanied by severe pain in the left forearm. I saw him approximately one hour after the circulatory accident and found that his arm from the upper third downwards was pulseless and cold. There was a distinct wax-like band encircling the arm about four or five centimeters above the elbow. Two hours after the onset of the attack the patient was taken to Garfield Hospital, where an embolectomy was performed by Doctor Kerr. Unfortunately, the patient suddenly died of coronary thrombosis before the circulation had been reestablished in his arm.

It is evident from the history of these two cases that an early diagnosis should be made and an immediate embolectomy should be performed in cases of arterial occlusion in the extremities to prevent the possibility of the development of gangrene. However, there is ever present the possibility, even after an embolectomy, of these patients dying of coronary occlusion.

Dr. Arthur M. Master, New York, N. Y.—The mortality following embolectomy is high. Although, as Dr. Conner has pointed out, this is in a large measure due to delay in performing the embolectomy operation there are times when conservative treatment is indicated. The surgeon should see the patient as promptly as possible. We have recently seen two patients, both women with mitral stenosis and auricular fibrillation, recover completely after embolism. In one case there was evidence of a saddle-shaped embolus at the bifurcation of the abdominal aorta and the patient's condition was so poor that the surgeon, Dr. Harold Neuhof, decided upon conservative treatment. In the other case the patient had an embolus to the right popliteal artery with resulting beginning gangrene of the toe tips, with absolute rest and dry heat she recovered completely.

Dr. G. Werley, El Paso, Texas.—Massage for the relief of arterial embolism is a valuable suggestion. This brings up the question of differential diagnosis. I had a case in point. A man aged 41 years, had mitral stenosis and for three years the heart had been fibrillating, when he suddenly suffered paralysis of his right leg. The leg was pale, cold, pulseless and quite painful, and general symptoms of shock were noted. The symptoms and signs pointed plainly to embolism and preparations were made for embolectomy. After about an hour faint pulsations appeared in the femoral artery, a distinct thrill was felt and sounds like those heard on taking blood pressure were heard. In a short time he was able to move his leg and next day he could walk about the room.

Two months later he died suddenly following what we thought was embolism at the base of the brain. Post mortem examination showed slight atheroma of the right iliac artery with some rugation of the intima. Microscopically the intima was detached from the subjacent tissues over a small area. There was softening of the pons due to complete thrombosis of the basilar artery. There was an ulcerated

atheromatous patch at the base of the median mitral leaflet, but no evidence of thrombi in the left auricle.

Before attempting embolectomy, the possibility of intermittent claudication or thrombosis should be considered.

Dr. Weiss.—Dr. Conner's remarks urging us to recognize embolic occlusions of arteries early and to instruct hospital interns for prompt action in calling in a surgical consultant are very important. It is also important that every hospital should have one or two surgeons specially trained in embolectomy. It is often not appreciated that, on the whole, the performance of the embolectomy over certain arteries of the extremities is a relatively simple operation. I also agree with those speakers who pointed out that not all the arterial emboli of the extremities lead necessarily to gangrene. In a certain number of instances, particularly if the occlusion is only partial and the rapid organization or recanalization of the embolus reopens the circulation, complete recovery follows. As mentioned in the paper, the degree of collateral circulation is also a determining factor.

As to the rôle of massage in case of embolism, I know nothing.

We have made a similar observation to that described by Dr. Fahr, namely, that at times in a patient who has suffered from auricular fibrillation for many years, without obvious reason an embolus develops, and following this at various time intervals a number of other emboli occur. While the occurrence of embolism in rheumatic heart disease, as well as in arteriosclerotic heart disease, is not rare, it is surprising how little these problems have been studied from the statistical and clinical points of view.

Discussion of papers by Dr. Anderson and Drs. Master and Jaffe.

Dr. Louis N. Katz, Chicago, Ill.—The report by Drs. Master and Jaffe emphasizes again the importance of the electrocardiogram in determining heart involvement in acute infectious diseases such as rheumatic fever. With the paucity of physical findings often present during the active stage of rheumatic fever the study of serial electrocardiograms should be of great assistance in determining the presence of heart involvement. While physicians have overemphasized the importance of the electrocardiogram in other conditions, they have erred in the opposite direction in acute infectious processes. The electrocardiogram is a very useful adjuvant in estimating the condition of the heart in rheumatic fever and should be employed oftener.

The idea presented by Dr. Anderson is an excellent one, but an examination of his records fails to prove his point. The electrocardiogram of the patient he showed is of the bundle-branch type and is therefore not specific for a recent coronary thrombosis, although it may very well be caused by such a process. The changes in the electrocardiogram in his animal experiments are slight and we have seen similar changes from day to day in the normal, unanesthetized animal. With the evidence at present available I fail to see that the electrocardiogram in pulmonary embolism resembles in any way the changes seen in recent coronary occlusion. I should like, therefore, to emphasize that in differentiating recent coronary occlusions from allied conditions, the electrocardiogram is one of the most useful fields of electrocardiology.

Dr. M. H. Dawson, New York, N. Y.—It is very useful from the clinical point of view to be able to distinguish rheumatic fever and rheumatoid arthritis so clearly. However one point should be mentioned, namely, that the average age of the rheumatic fever patients studied was ten years younger than the rheumatoid arthritis group. It is well known that the degree of cardiac involvement in rheumatic fever

varies with the age of onset of the disease. Before definite conclusions are drawn, I think it is important that the average ages of the two groups should be comparable.

Dr. Master.—My cases did not include children. The youngest patient was thirteen years of age. I do not know what the same kind of investigation in children would show. I must repeat, however, that in adults one type of acute polyarthritis shows definite evidence of cardiac involvement, the other practically none.

Discussion of paper by Dr. Nichol.

Dr. B. S. Oppenheimer, New York, N. Y.—The data on rheumatic heart disease in Miami presented by Dr. Nichol is valuable, especially to those of us in the North who send patients who have suffered from rheumatic fever to the South. It is one of the important functions of the American Heart Association to stimulate interest in collecting facts on the geographical distribution of heart disease. It is disappointing to learn that a few cases of rheumatic heart disease have originated in Florida itself, even if the percentage of such cases among natives is very low. As to convalescence, it is worth noting that something may be accomplished, but apparently only temporarily, by sending the cardiac children who live under poor hygienic conditions to convalescent homes in the suburbs. The Mary Zinn Home for convalescent cardiac children ran for about seven years, just outside New York City. During their prolonged stay there the children gained in weight and height, and many of them had a healthy color, but on returning to their homes in the poor quarters of New York, they had about as many recurrences as the children who merely went to cardiac clinics, but never had had the opportunity of staying at a convalescent home.

Dr. T. Duckett Jones, Boston, Mass.—It has been my good fortune to have been associated for the past three years with Dr. C. F. Roche of Miami Beach, Florida, in transporting children with rheumatic fever and rheumatic heart disease to the St. Francis Hospital at Miami Beach. These children on the whole have recovered more rapidly in southern Florida than in New England. However, there have been recurrences of rheumatic fever among the group in Florida. This has happened despite the seeming rarity of hemolytic streptococcus infections in that vicinity and among the group. Dr. Nichol's paper is a very interesting one. It would seem to me, however, that it would be wise to limit the term "native" to those children who have never been out of southern Florida and those who rarely come in contact with tourists. With the large number of tourists annually, a large portion of the native population must come in contact with the causative agent of rheumatic fever, whatever it might be.

Dr. Nichol.—I am glad that Dr. Jones showed some pictures depicting the changed appearance of some of the rheumatic heart children after their stay in Florida. The point worth emphasizing, apart from the effect on the patient, is the infrequency of rheumatic heart disease *originating* in Miami, although some cases undoubtedly do arise there.

Discussion of paper by Drs. Jones and Bland.

Dr. W. D. Stroud, Philadelphia, Pa.—This report by Drs. Jones and Bland of their observations upon children and adults with rheumatic fever in Boston, should prove most valuable. It is interesting to note that in a similar group of individuals suffering from rheumatic heart disease in Bristol, England, Carey Coombs found a mortality of 21.4 per cent, while Dr. Jones, I believe, reported a mortality of 21 per cent. We have gained the same impression as that expressed by Dr. Oppen-

heimer, that the majority of these children, while they are in our convalescent hospital, have improved quite rapidly but that upon returning to their home environment, they seem to develop reactivations of their rheumatic fever just as frequently as children who have not had the care which our hospital affords. Perhaps their reactivations are not as severe, however.

Dr. Hugh McCulloch, Saint Louis, Mo.—We have studied the subsequent course of cardiac children who have had convalescent care in an institution. The results of this study showed that when they were discharged home, many of them showed attacks of rheumatic manifestations that were as frequent, or more frequent, than a group of rheumatic cardiac children who were under observation in the out-patient department and who had not been admitted to the institution. Our impression in this study was that the attacks suffered by the institutional group were shorter and less severe than those occurring in the home care group. We felt the institutional group had benefited by the care given them and that they were better able to go through these recurring attacks. It was very obvious in the study that the follow-up care of the institutional group is extremely important; that without strict medical and social supervision of the child after his return home with regulation of his various activities, all the benefits of institutional care would be lost.

Dr. Jones.—I would agree that the average age of onset of any group of patients will vary considerably depending upon the average age of the group being studied. It might also be pointed out that a satisfactory history of onset of rheumatic fever is rarely obtained from a middle-aged rheumatic. The onset may be so mild as to be completely forgotten even should the patient have been cognizant of it at the time. I feel that at present we cannot tell just what rôle chorea plays in rheumatic fever, or whether all chorea is rheumatic fever. It is evident, however, that as a rule chorea is closely associated with rheumatic fever, and that it seems to occur in those patients who do well clinically. Chorea alone without a history of rheumatic fever manifestations and without laboratory evidence of infection, rarely develops clinically evident heart disease. Conversely, those patients having rheumatic fever and later chorea or exhibiting manifestations of both conditions simultaneously will remain free from clinical evidence of heart disease in a larger percentage than the group who develop rheumatic fever following chorea. At the present time we cannot completely dissociate rheumatic fever and chorea.

Department of Reviews and Abstracts

Critical Review

THE ORIGIN OF THE HEART'S "INTERNAL STIMULUS"*

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THE heart of either a cold or a warm blooded animal is able to maintain strong, rhythmical beats for a long time after all nervous, vascular, and supportive connections between the heart and the rest of the animal's body have been severed provided the heart is perfused with a liquid containing certain inorganic salts in proper proportion. To explain this automaticity of the heart many theories have been advanced. Those based upon a more modern conception of physics and chemistry date from about 1870. Attention has been directed toward the various factors supposedly capable of calling out the heart beat—the so-called "inner stimulus"—in a somewhat cyclic manner: toward first the organic constituents, then the inorganic, next the possible physicochemical arrangements of both organic and inorganic, again toward the organic, and at the present time there is a renewed interest in the inorganic constituents with respect to their possible rôle in releasing the heart beat.

Langerdorf[30] advanced a theory that the inner stimulus controlling the automaticity of the heart arises from cleavage processes within the heart, probably in the ganglion cells—"Der Lebensproduckt der Zelle is ihr Erreger." This stimulus originates in the catabolism of the cells, and anabolic processes are assumed to diminish its production. Thus, adopting a view earlier expressed by Gaskell, the inhibitory nerves produce their effects by increasing the anabolic processes. Assuming a constant production of this stimulating substance, he explained the rhythmicity on Rosenthal's hypothesis of a steady stimulus opposed by a steady resistance. Langendorf placed the burden of calling out the heart's rhythmic beats upon the organic constituents of the heart and assigned to the inorganic cations, sodium, potassium, and calcium, the minor rôle of placing the cardiac musculature in proper condition for the action of the inner stimulus.

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Englemann,[19] basing his views mainly upon a study of the automaticity of the venous end of the heart, believed that a stimulating substance responsible for the inner stimulus is formed as a result of the resting metabolism of the heart. The accumulation of this material during the pause suffices eventually to bring on a systolic contraction. The diastolic pause in its duration is the reciprocal of the rate of development of the stimulating substance. To explain the rhythmicity it is suggested that each systolic contraction causes a diminution or neutralization of the stimulating substance. These views of both Langendorf and Englemann are entirely theoretical inasmuch as nothing of the nature of direct proof is given for existence of such a stimulating substance in the heart.

Ringer[44] noted that if an excised heart is perfused with an aqueous solution of the salts of sodium, calcium, and potassium in the concentration in which these salts are found in the animal's blood, a rhythmical, functional beat may be obtained for a long time. He believed that no artificial perfusion fluid could so function unless it contained the salts of these cations and from this reasoned that an interaction of these inorganic salts is a necessary condition for the heart beat. He emphasized an antagonistic action of calcium and potassium upon the tone of the cardiac musculature and suggested that calcium elicits the contraction of the heart's tissues while potassium brings about their relaxation.

Loeb[33] observed that the presence of certain ions influences the imbibition of water by soaps and that variations of the kind and concentration of these ions within the soap can cause water to proceed into or out of the soap. He further noted that changing the kind and concentration of these same ions in the fluid bathing an excised skeletal muscle can vary the activities of this muscle. These observations led him to postulate a mechanism by which ionic activity serves to release the spontaneous, rhythmic contractions which can be called forth in skeletal muscle under certain conditions. He expressed the conviction that the same mechanism can be extended to cardiac musculature. According to Loeb's theory, the various ions exert their influence by entering the cell and uniting with certain cellular constituents. Acting as the principal agent in initiating automaticity, the sodium ion enters the cell and displaces a small portion of the calcium ion from its intracellular compounds and by this displacement excites the muscle to contract. If this displacement proceeds too far, the sodium ion "poisons" the tissue. In this theory of the origin of the heart's automaticity Lingle concurred.

Howell[25] advanced a theory in which an antagonism between sodium and calcium present in balanced ratio acts as the exciting agent for spontaneous beats rather than the activity of sodium alone as Loeb

believed. Howell denied the "poisoning" action of sodium upon cardiac tissue except so far as any single known substance is likewise poisonous in being unable to support rhythmic beats when used alone. Warburg[48] has recently shown, however, a so-called toxic action of sodium chloride upon certain cells in that their oxidations are greatly increased when sodium chloride is the only salt contained in the fluid surrounding them; furthermore, this increased oxidation is neutralized by the addition of calcium salts or of sodium cyanide to the fluid in contact with the cells. Loeb, Lingle, and Howell agree in assigning no direct action in the production of the inner stimulus to potassium. It should be borne in mind that rhythmicity at this time was defined wholly in terms of mechanical contractions.

Zwaardemaker,[50] however, placed the responsibility of initiating the heart's spontaneous rhythm upon potassium. While holding sodium, calcium, and potassium as essential to the maintenance of a rhythmic beat, he asserted that the radiations emanating from the potassium act directly upon the heart's musculature stimulating it to its rhythmic contractions. His modified view of the behavior of potassium will be noted in connection with the heart hormone theory. He held that potassium can be replaced in its effect by any other radioactive substance. He divided the radioactive substances into two groups dependent upon the nature of their emanations, soft alpha or hard beta rays, and asserted that the two groups are antagonistic to each other in their effects upon the heart. This specific rôle assigned to potassium in calling out the heart beat has been criticized by Clark[10] and by Libbrecht,[31] while Zeehuisen[49] has shown that failure of the heart's rhythmicity is not directly connected with the removal of potassium from the heart's tissues.

Mines[38] advanced an interesting and rather comprehensive physicochemical theory to account for the origin of the heart beat. He assumes that the contractile mechanism responds to a transitory increase of hydrogen ions at interfaces within the cardiac muscle structure. Such a change in hydrogen ion concentration will be dependent upon the maintenance of a certain degree of permeability of the cell surfaces or cell membranes. Maintenance of this proper degree of permeability is a function both of the chemical composition of the cell membrane and of the electrical potential existing across the membrane itself. He has classed the calcium ion as a combining ion, capable of entering into chemical union with the membrane itself and exerting an influence upon its permeability. The sodium and potassium ions he has classed as nomadic ions because of their supposed ability to penetrate the cell membrane and by such migrations exert an influence upon the electrical charge of different parts of the cell. The hydrogen and hydroxyl ions he classes as polarizing ions which affect the

surface potential of the cell through adsorption. Hogben[24] has also furnished experimental evidence in confirmation of this view.

Clark[9] has advocated a somewhat similar theory in which lipoids become essential constituents of the cell surfaces. The function of calcium is to vary the colloidal state of this lipoid-containing cell surface. The permeability of the cell to electrolytes is made dependent on, or influenced by, the presence of calcium and lipoids at the cell surface. Clowes[11] has constructed a model in which both conductivity and permeability of a membrane soaked in an emulsion of oil and balanced soap solution vary with changes in the calcium to sodium and potassium ratio due to the degree of externalization of the lipoid phase of the cell membranes. Osterhout[40] made a like observation with living plant tissues. Rona and Petow[45] explain the mutual antagonism of calcium and potassium upon the basis of opposed influences in the externalization of the lipoid phase of cell membranes.

Andrus and Carter[1] have elaborated a physicochemical theory in which the hydrogen ion concentration in different parts of the cell explains the origin of the heart beat. The cardiac rhythm, according to these investigators, is due to the rhythmic building up and discharging of a potential difference across a semipermeable membrane. The rate of discharge and the magnitude of this potential difference are dependent fundamentally upon the difference in hydrogen ion concentration within the cardiac tissues and the fluid bathing them. The level of the potential difference at which this discharge takes place is determined by the permeability of the interposed membrane which is in turn dependent upon the concentration of the sodium, calcium, and potassium salts on either side of the membrane. Mention must be made of a belief that carbon dioxide acts as the internal stimulus itself. This view was first advanced by Martin[36] and has been elaborated by Mansfeld and Szent-Györgyi.[35]

Lillie[32] explains the heart's automaticity on the basis of alternation between states of activity and passivity perhaps of the nature of oxidation-reduction reactions. He has constructed inorganic models capable of exhibiting such phenomena as chronaxia, electrotonus, polar stimulation, inhibition, and refractory period in close agreement with living systems.

Zwaardemaker[51] altered his original theory in which potassium by its radioactivity stimulates the heart tissue directly to one in which a hormone manufactured by the skeletal muscle is changed by the radioactivity of potassium to a substance (automatin) which is capable of imparting automaticity to the cardiac tissue. Haberlandt[23] has proposed a similar theory in which a hormone is formed constantly by the conducting tissues of the heart and is responsible for the cardiac contractions. He explains alternate contraction and relaxation as

a function of the refractory period of the heart cells. Demoor[15] has advanced a somewhat different humoral theory. According to his view, the myocardium is capable of giving automatic contractions but the contractions are irregular. Under the influence of a substance elaborated particularly by the nodal tissue the myocardium assumes regularity. His theory is based chiefly upon the observation that the right auricle of the rabbit excised and dropped into a Ringer-Locke solution soon assumes a regular rhythm; the left auricle, however, gives only aperiodic, jerky beats in this solution. If now the solution in which the right auricle has been active for a while is poured over the left auricle, the latter assumes rhythmical beats. We have been able to confirm this observation in about 70 per cent of trials. (Preliminary publication, Proc. Soc. Exper. Biol. & Med. **30**: 786, 1933.) Demoor has postulated other heart hormones which bring about augmentation and inhibition of the heart. The "specificity" of these substances has been questioned since extracts of other tissues have been shown to have similar effects upon the heart tissue. Asher and Beyeler,[3] Granit and von Bonsdorff,[22] Katz and Liebensohn,[27] Rigler and Singer,[41] Rigler and Tiemann,[42] Oppenheimer,[39] Kraut, Frey, and Werle,[29] Thorpe,[47] Cannon and Griffith,[7] and Chang and Chen[8] have demonstrated that such substances have a wide distribution in the tissues.

With the development of instruments capable of measuring the electrical variations that occur in connection with the mechanical movements in contracting musculature there has been made available a new criterion for the presence or absence of contractions in a heart. It was long supposed that the electrical phenomena were concerned perhaps solely with the internal stimulus and definitely preceded any distortion of the muscle substance. Einthoven,[17] Einthoven and Hügenholtz,[18] Arbeiter,[2] and de Jongh[14] have advanced the idea that electrical and mechanical phenomena are indissoluble; while Gasser and Hill,[21] Rijlant,[43] Kleinknecht,[28] Fulton,[20] Jolles,[26] Bishop and Gilsen,[5] Max,[37] and Baetjer and McDonald[4] have presented evidence that the two may be separated.

Without much speculation upon the actual origin of the electrical variation shown by the beating heart, Craib[12] has called into question the usual method of explaining this variation upon the basis of a state of negativity which is developed by acting tissue as compared to that of resting tissue. He offers mathematical and experimental proof that the electrical phenomena of the heart partake of the nature of what he terms "electrical doublets" and defines an electrical doublet as two closely adjacent poles situated within a conducting medium and maintained at equal and opposite potentials.

At any rate, since the electrical phenomena in connection with the heart's contraction may be used as a means of measuring the heart's

activity, the functional importance of the inorganic ions in the production of the internal stimulus has become a subject for reinvestigation. Briefly stated, it appears that according to the present view sodium is perhaps most intimately concerned with actual release of the internal stimulus, calcium with the strength of contraction, and potassium with the counteracting of an irritating antagonism between sodium and calcium. Reference may be made to Clark,[10] Arbeiter,[2] Ten Cate,[46] Hogben,[24] McDonald,[34] Zeehuisen,[49] Colle,[13] Bouckaert and Belehradek,[6] Zwaardemaker,[51] Max,[37] and Baetjer and McDonald.[4]

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Selected Abstracts

Wood, Francis Clark and Wolferth, Charles C.: Experimental Coronary Occlusion. Arch. Int. Med. **51**: 771, 1933.

The dog presents a situation analogous to that existing in man, with respect to occlusion of the coronary arteries. Infarction in some parts of the heart produces a deviation of the RS-T interval from the isoelectric line in the conventional electrocardiogram. Infarction in other parts of the heart does not.

Electrograms show that the failure of certain infarcts to affect the limb lead electrocardiogram is not due to a failure of the development of changes in the action current in the infarcted area. By means of direct heart leads, deviations of the RS-T interval are recordable within a few minutes after infarction of any part of the surface of the heart.

If conduction from all surfaces of the heart is adequate and if an anteroposterior chest lead is used in addition to the routine limb leads, a deviation of the RS-T interval can be recorded in one or more leads after occlusion of any one of the three main coronary arterial trunks. This is likewise true of occlusion of some of the branches of these arteries.

Deviation of the RS-T interval due to occlusion of the left anterior descending coronary artery appears in only one of these four leads, the anteroposterior chest lead. Likewise, in man, infarcts in some parts of the heart fail to produce deviations of the RS-T interval except in certain leads which heretofore have not been used as a routine measure.

When the right and the left arm lead wires are used and when the electrodes are placed on opposite sides of the chest, an infarct located beneath the former produces a depression of the RS-T interval; one located beneath the latter produces an elevation of this interval. The direction of the deviation of the RS-T interval and the lead in which it makes its maximum appearance serve to indicate the location of the infarct. It is therefore probable that more accurate electrocardiographic localization of myocardial infarcts may be attained in man by the use of chest leads in addition to the three conventional ones.

Deviations of the RS-T interval after coronary occlusion in the dog appear within two minutes. It is not likely that they take much longer to appear in man.

No additional impairment of the coronary circulation or of the general circulation is necessary for the production of deviation of the RS-T interval beyond that produced by occlusion of a coronary artery.

The size of an infarct necessary to cause changes in the RS-T interval, recordable from the body surface, has not been determined accurately. It is certain, however, that relatively small infarcts suffice. The optimum points of application of the electrodes for recording electrocardiographic changes after obstruction of the various coronary arteries deserve further investigation.

This series of experiments demonstrates that in the dog deviation of the RS-T interval from the isoelectric line is a characteristic result of acute infarction of any part of the surface of the heart. Failure to record this electrocardiographic change in previous similar experiments has often been due to failure to apply the electrodes to the surface of the body in the proper locations.

The necessity for augmenting the three conventional leads is apparent if a more nearly adequate electrocardiographic picture of cardiac events is to be obtained.

The authors also point out the relative immediate danger to the dog of clamping the various coronary arteries. Ventricular fibrillation is the usual terminal event in experiments on coronary occlusion. It occurs most rapidly when the left posterior circumflex artery is occluded, within three or four minutes as a rule. It develops more slowly after obstruction of the left anterior descending artery. The least danger of early fibrillation seems to result from right coronary occlusion. Clamping of both the right and the left anterior descending arteries did not seem to be as immediately dangerous to the life of the animal as clamping of the left posterior circumflex alone. The authors do not understand the reason why occlusion of the latter artery should be particularly prone to cause ventricular fibrillation. The question arises as to whether there is an area in the distribution of this artery which, when deprived of its blood supply, is especially likely to cause fibrillation of the ventricles. The coronary sinus and the inferior vena cava may be clamped for relatively long periods without endangering the life of the animal.

Barton, E. M., and Greenwood, H. H.: Experimental Infarction of the Interventricular Septum of the Canine Heart. Arch. Path. 16: 15, 1933.

When the front septal branch of the left coronary artery of the dog was occluded by ligation and when the animals had recovered from the immediate effects of the operation, a typical infarct was produced in the interventricular septum and usually in part of the auriculoventricular node as well. Some of the ganglion cells and ganglion cell groups in such infarcted nodes had undergone degenerative changes.

No permanent interruption of conduction as a result of these lesions was discoverable by electrocardiograms. Mural thrombosis of the cavities of the heart was not observed. Among the possible reasons for the paucity of the conduction disturbances are the richness and the variability in the arterial blood supply to the conduction system of the dog and the frequency with which the endocardium and the Purkinje fibers over the infarcts were found intact.

Dock, William: Mode of Production of the First Heart Sound. Arch. Int. Med. 51: 737, 1933.

Experiments on the exposed hearts of dogs demonstrate that there is no muscular element in the first heart sound and that ventricular systole produces no audible vibrations, in either empty or full hearts, if tensing of the auriculoventricular valves is prevented.

A comparison of the pressure changes in the auricles and the rate of outflow through the atrioventricular valves with the period at which first sounds are accentuated by a previous auricular systole shows the importance of the position of the auriculoventricular valves in determining the loudness of the first sound. If the valves are closed and intraventricular pressure about as high as that in the auricle, ventricular systole causes only a faint sound; if the valves are slack and displaced toward the ventricle by the rush of blood through them, ventricular systole produces a loud first sound.

The author, therefore, concludes that the first heart sound is due to suddenly putting under high tension the previously slack fibers of the auriculoventricular valves. If the valves are closed and the slackness is taken up gradually before

ventricular systole occurs, the intensity of the sound is greatly diminished. The factors determining loudness of the first sound are, therefore, the degree of tension in the valves when ventricular systole occurs and the rate of rise of intraventricular tension.

Greene, J. A., and Coggeshall, H. C.: Clinical Studies on Respiration. I. The Plethysmographic Study of Quiet Breathing and of the Influences of Some Ordinary Activities on the Expiratory Position of the Chest in Man. Arch. Int. Med. **52**: 44, 1933.

The plethysmographic method for the study of the respiratory movements in man has been described. The false results obtained by the method are discussed.

The expiratory position of the chest in repose is more constant than the inspiratory position, but the expiratory position may also fluctuate in apparently normal subjects. After the subject has become accustomed to the procedure, the volume of air in the lungs at the end of expiration increases immediately when the body is changed from the horizontal to the vertical position and decreases immediately when the body is returned to the horizontal position. The expiratory position of the chest may or may not increase with slight muscular work. If it increases, the time required for it to return to its previous level varies. The expiratory position of the chest and the depth of the respirations during talking and reading aloud appear to depend on the length of the sentences and phrases when the subject is at ease and when hyperventilation may occur.

Greene, J. A., and Coggeshall, H. C.: Clinical Studies of Respiration. II. Influence of Determination of Basal Metabolism on Respiratory Movements in Man, and Effect of These Alterations on Calculated Basal Metabolic Rate. Arch. Int. Med **52**: 226, 1933.

The influence of the determination of the basal metabolic rate on the respiratory movements has been studied in three normal and twenty diseased subjects. The respiratory movements may be altered in rate, rhythm, amplitude, or expiratory position of the chest, or in several combinations of these. The respiratory movements were altered in every subject during the determination of the basal metabolic rate, and the ventilation was increased in twenty subjects, unchanged in one, and questionably altered in two. The manner in which the respiratory movements are altered varies with different subjects and may vary with the same subject during different examinations. Changes in the expiratory position of the chest may alter the basal metabolic rate as determined by the closed circuit method. The decreased excretion of carbon dioxide by some subjects in the basal state may be due in part to changes of the expiratory position of the chest.

Alterations of the expiratory position of the chest may explain some of the variances between the determinations of the basal metabolic rate and the clinical findings. The alterations in the determinations of the basal metabolic rate due to changes of the expiratory position of the chest would be materially decreased if longer test periods were used.

Hurtado, Alberto, and Boller, Charles: Studies of Total Pulmonary Capacity and Its Subdivisions. I. Normal, Absolute and Relative Values. J. Clin. Investigation **12**: 793, 1933.

Determinations of total pulmonary capacity and its subdivisions have been made in fifty normal young males. Christie's method of oxygen dilution without

forced breathing was used, and his classification adopted. All determinations have been made with the subject in a recumbent position after a preliminary period of rest. The age and physical characteristics of the subjects are fully presented.

The results obtained suggest that there are wide variations in the absolute values of the total pulmonary capacity and its subdivisions. The vital capacity, residual air, and midcapacity fluctuate within well-defined limits if expressed as a percentage of the total volume. If the vital capacity is less than 65 per cent of the total volume, or if similarly the residual air is higher than 35 per cent, an impairment in the alveolar ventilation must be suspected.

The constant normal ratios found between the total pulmonary capacity and its main subdivisions suggest that alterations in these ratios may give a quantitative estimation of the degree of functional respiratory efficiency from the point of view of alveolar ventilation.

Hurtado, Alberto, and Fray, Walter W.: Studies of Total Pulmonary Capacity and Its Subdivisions. II. Correlation With Physical and Radiological Measurements. J. Clin. Investigation **12**: 807, 1933.

In the present communication the correlations between the total capacity and its main subdivisions with height, weight, surface area, and external and radiological measurements of the thorax are discussed. It has been shown that they may be calculated best in a given case from the so-called radiological chest volume. The method of calculation is fully presented. Comparison of the observed and the calculated volumes shows a very close correspondence. The application of these observations allows one to recognize pathological deviations. Studies have been made of the normal variability in the degree of expansion of the chest which is best exhibited by measurements of the chest film taken by means of a standard, the technic of which has been described. The same film together with the measurement of the anteroposterior diameter of the chest at maximum inspiration furnished all necessary information for the calculation of a given pulmonary capacity if correlation, coefficients, and regression formulas are used. The influence of the shape of the chest has also been investigated. The observations lead to the following conclusions:

When the total pulmonary capacity and its main subdivisions are calculated on the basis of the radiological chest volume, at maximum inspiration, the following deviations in the observed values (as compared with the calculated ones) are considered to be significant: a difference of over 15 per cent in the total pulmonary capacity and vital capacity and of 30 per cent and 40 per cent in the midcapacity and residual air respectively.

If the ratio: (Area at maximum expiration/Area at maximum inspiration) x 100 is higher than 72.0, a reduction in chest expansion is indicated. Further evidence of deficient expansion is obtained if the diaphragmatic excursion, the lateral expansion, and the degree of movement of the ribs are found to be less than 4 cm., 2 cm., and 12° respectively.

There is a certain correlation between the degree of chest expansion (as appreciated by the ratio mentioned) and the relative proportions of subdivisions of the pulmonary capacity. Deficient expansion tends to be accompanied by a higher percentage of the residual air in relation to the total capacity.

There is a relationship between the shape of the chest and the capacity of the lungs. Persons with broad, muscular chests and high diaphragms (hypersthenic type) usually present low volumes of reserve air, as compared with long and narrow-chested persons with low diaphragms (asthenic type). The latter have larger thoracic capacity and consequently larger pulmonary capacity.

From the observations made on normal males, it is possible to detect pathological changes in the absolute and relative pulmonary capacity in a given case. The importance of recognizing such alterations is obvious.

Hurtado, Alberto, and Fray, Walter W.: Studies of Total Pulmonary Capacity and Its Subdivisions. III. Changes With Body Posture. J. Clin. Investigation 12: 825, 1933.

The effects of posture upon the pulmonary capacity and the size and expansion of the chest have been observed in ten healthy males by comparing measurements made in recumbent and sitting postures. It has been found that when recumbent there are slight decreases in the total volume, the vital capacity, and the residual air, but the reserve air decreases markedly. On the other hand, there is a marked increase in the volume of the complementary air. Similar and parallel decreases, although proportionally less marked, have been demonstrated to occur in the size of the chest. This diminution is most marked at midcapacity, and it is caused by an upward displacement of the diaphragm. An analysis of the expansion of the chest in both sitting and recumbent positions shows also parallel changes. In the latter posture the diaphragmatic excursion and the change in the area of the projection of the lungs corresponding to the reserve air are considerably reduced, while the reverse is true in relation to the complementary air.

These observations furnish additional data regarding the close correlation existing between the pulmonary capacity and the size and expansion of the chest and indicate the necessity for adopting a standard posture when investigations of this nature are made.

Hurtado, Alberto, Fray, Walter W., and McCann, William S.: Studies of Total Pulmonary Capacity and Its Subdivisions. IV. Preliminary Observations on Cases of Pulmonary Emphysema and of Pneumoconiosis. J. Clin. Investigation 12: 833, 1933.

In seven of nine cases of pulmonary emphysema, the total pulmonary capacity observed corresponded closely with that predicted from measurements of the chest cavity. In two it was slightly less. Increase in the volume of the residual air and a corresponding reduction in the vital capacity was observed in all the cases. In emphysematous patients there was a definite reduction in expansion of the chest, the degree being closely correlated with alterations in the relative pulmonary capacities.

In cases of pneumoconiosis, the total capacity of the lungs observed was less than that predicted from measurements of the chest due to decrease in the vital capacity. The residual air was moderately increased in four of five cases. In one the changes were minimal. Decrease in expansion of the chest was not a significant feature of cases of pneumoconiosis. Cases in which the ratio was abnormally high were found to exhibit low saturation of the arterial blood with oxygen, indicating poor alveolar ventilation.

Preliminary observations on response to exercise showed that the capacity to ventilate the lungs was limited in a severe case of emphysema and in one of pneumoconiosis compared with that in a normal man. Further observations will be necessary to establish a relationship between the degree of functional disability and abnormalities in pulmonary capacity.

Coburn, Alvin F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues. Am. J. Dis. Child. 45: 933, 1933.

The present study has been made on a group of 320 patients who died with rheumatic disease and who were examined post mortem. Particular interest is in a group in which death occurred during activity of the rheumatic process, showing alterations in the tissues as a result of the rheumatic infection. Hemorrhagic lesions without distinctive histologic structure were conspicuous. The character of these nonspecific lesions suggested the activity of a single process with varying degrees of intensity: (1) engorgement of the blood vessels; (2) alteration in the permeability of the vascular tissues with diapedesis, but without a demonstrable change in the structure; (3) an inflammatory reaction. The damage to the tissue in the patients with acute rheumatism was characterized by the absence of detectable microorganisms and commonly by vasodilatation, swelling of the endothelium, necrosis of the collagen, infiltration with various wandering cells, and especially hemorrhage. During the first cycle of the rheumatic attack, few or no Aschoff bodies were detected in the cardiac muscle; however, the presence of specific lesions in the endocardium established the diagnosis.

When the rheumatic subject is infected with the hemolytic streptococcus, the initial response is of the usual clinical character. If the infection is limited to the upper respiratory tract, recovery occurs within a few days. This illness, though mild, may nevertheless be the first phase in the development of a severe rheumatic attack.

Following the subsidence of the local infection, the patient usually regains his customary health, and nothing abnormal is detected clinically. This quiescent interval of days or a few weeks represents the second phase in the evolution of the rheumatic process. The second phase persists until a rise in the titer of immune bodies is detected in the blood of the peripheral circulation. Almost simultaneously with this response of the immunity mechanism, the rheumatic process is activated in susceptible persons.

When the rheumatic process is activated, the initial response is characterized by manifestations of a hemorrhagic nature. Particularly common at this stage are epistaxis and the erythemas; while melena, hemoptysis, and hematemesis also occur. Studies of the excretion of erythrocytes in the urine indicate the close relationship of hemorrhage to the activity of the rheumatic process. Late in the attack, when symptoms are subsiding and the abnormal urinary observations have disappeared, there may be a second stage, characterized clinically perhaps only by the appearance of subcutaneous nodules.

The author believes, therefore, that the evolution of rheumatic fever consists of, first, a phase in which there is an infection of the respiratory tract with a hemolytic streptococcus, and second, a symptom-free phase in which the immune response develops in the rheumatic subject, and finally, the acute attack. During the third phase, activity of the rheumatic process is characterized clinically by a tendency to hemorrhage which was well correlated with the anatomic observations in the cases studied.

Grollman, Arthur, Friedman, Ben, Clark, Gurney, and Harrison, T. R.: Studies in Congestive Heart Failure. XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients With Cardiac Disease. J. Clin. Investigation 12: 751, 1933.

A critical study has been made of the possible sources of error of the Burwell-Robinson, venous plateau, and acetylene methods for measuring the cardiac out-

put which may invalidate the results obtained when applying them to patients with congestive heart failure. The methods to be used for detecting and avoiding these errors are indicated. Results as obtained by these different methods are given.

As to the relative merits of the method studied, the laboriousness of the Burwell-Robinson and venous plateau methods both to the patient and to the investigator renders them inferior to the relatively simple acetylene procedure. In persons with normal arterial oxygen saturation, the practice of taking three samples as advocated for the acetylene method should exclude the possibility of error. With care, moreover, the method will be found to be applicable to a large percentage of subjects with advanced cardiac disease and with mild congestive failure. In those subjects in whom the method is not applicable, the venous plateau method may be applied. Unfortunately, it is in these very cases that the pitfalls inherent in the latter method occur and great care and labor are required to avoid them.

Wolff, Louis: Angina Pectoris (or Status Anginosus) and Cardiac Asthma Induced by Paroxysmal Auricular Fibrillation and Paroxysmal Tachycardia. New England J. Med. **208**: 1194, 1933.

The author describes four patients in whom angina pectoris (or status anginosus) and cardiac asthma were induced by paroxysmal auricular fibrillation and paroxysmal tachycardia. This condition should be differentiated from angina of effort in coronary thrombosis, and the difficulties encountered in such differentiation are discussed. Embolism, fever and leucocytosis may sometimes occur with or follow paroxysmal arrhythmias and consideration which must be reckoned with in the study of patients with pain suggestive of coronary thrombosis.

The cardiovascular changes which occur during a paroxysmal arrhythmia favor vascular thrombosis, and it must be recognized that in the face of coronary artery disease, coronary thrombosis may be induced by paroxysm of rapid heart action. The prevention or curtailment of such paroxysms by quinidine and other methods offers a prophylactic measure against coronary thrombosis in a small number of patients.

Sproull, John: The Simulation of Coronary Thrombosis by Angina Pectoris Induced by Paroxysmal Tachycardia. New England J. Med. **208**: 1198, 1933.

Two cases of angina pectoris induced by paroxysmal tachycardia and closely resembling cases of coronary thrombosis are reported. Because of the difficulties of establishing a diagnosis of paroxysmal tachycardia as a cause of angina pectoris, it appears that the proper and safe procedure is to treat suspected cases as if coronary thrombosis were present, reserving the ultimate diagnosis until all possible evidence has been accumulated and considered. On account of the similarity of the two conditions and also for the reason of the variation in their prognosis and care, a complacent acceptance of the diagnosis of coronary thrombosis in attacks of severe angina pectoris with tachycardia is to be avoided. As in other instances, the failure to have the condition in mind causes some errors in diagnosis.

Ayman, David: The Personality Type of Patients With Arteriolar Essential Hypertension. Am. J. M. Sc. **186**: 213, 1933.

A study has been made of the personality of 182 patients consisting of middle-aged hypertensive patients, hypertensive patients between the ages of eighteen

and thirty-five, middle-aged normal subjects with normal blood pressure, and young normal subjects with normal blood pressure. The results indicate that hypertensive subjects tend to have a distinct type of personality. Their personality is characterized by increased psychomotor activity. They are dynamic, hyperactive individuals with a large and steady output of energy. They tend to be sensitive and quick-tempered. The mood fluctuations, however, are not an important feature, which differentiates them from the manic-depressive individuals. The hypertensive personality has existed as far back as the subject can remember.

Lundy, Clayton J., and Bacon, Charles M.: Premature Left Ventricular Beats From Electrical Stimulation of Exposed Human Heart. Arch. Int. Med. 52: 30, 1933.

The authors had the opportunity of studying a four-year-old child in whom a purulent pericardial effusion developed following influenza of the upper respiratory tract, and pericardiotomy had been performed through the left half of the sternum, at the level of the fourth and fifth rib. Through the operative wound could be seen the left auricular appendix and the basal portion of the left side of the ventricles.

Electrically induced extrasystoles from the base and apex of the left ventricle gave discordant QRS complexes. The extrasystoles arising from the base were upright in Lead I and inverted in Lead III. Those arising from the apex were inverted in Lead I and upright in Lead III. The ventricular extrasystoles elicited from a point designated as I is from a region heretofore unexplored.

Ayman, David, and Krakower, A.: Influence of Sclerotic Arterial Wall on Blood Pressure Measurements. Arch. Int. Med. 52: 33, 1933.

Simultaneous bilateral readings of the blood pressure in the radial arteries were made in a patient who both clinically and radiographically had a soft radial vessel on one side and a sclerotic radial vessel on the other side. The results are in accord with evidence obtained previously in studies with excised vessels, and the observations indicate that the sclerotic arterial wall has no significant effect on the determination of blood pressure. It was also found that in this patient, as well as in three other patients with marked radial sclerosis, the radial blood pressure reading was higher than the brachial blood pressure reading.

Solomon, Philip, Hurwitz, David, Woodall, Martin, and Lamb, Marion E.: Diagnosis of Gonococcus Endocarditis. Arch. Int. Med. 52: 1, 1933.

A case of gonococcus endocarditis is reported in detail. The diagnosis of acute vegetative endocarditis was made clinically and was proved at autopsy. The organism grown from the blood stream and from the vegetation on the aortic valve post mortem was identified as a gonococcus by its morphologic and cultural characteristics, fermentation reactions, agglutination, precipitin, and complement fixation reaction.

The condition occurred in a patient during the last days of pregnancy with symptoms of an upper respiratory tract infection. Following a bronchopneumonia, the temperature continued high and the pulse rate rose to 140. Two days later chills and hemiplegia and signs of endocarditis developed. The spinal fluid was blood tinged and had 4,000 white blood cells per cubic millimeter. The organisms

were not recovered from the meningeal fluid. It is pointed out that gonococcus septicemia occurs fairly frequently and often is followed by recovery, but when endocarditis develops, the issue is grave.

Kugel, M. A., and Lichtman, S. S.: Factors Causing Clinical Jaundice in Heart Disease. Arch. Int. Med. 52: 16, 1933.

Two factors, the duration and the type of myocardial failure, are mainly responsible for the occurrence of pulmonary infarction. The lowest incidence of infarction occurred in patients with subacute bacterial endocarditis in whom congestive heart failure rarely occurs, and in those with primary failure of the right side of the heart, in whom the left side is usually competent until the end. The highest incidence occurred in the group with rheumatic cardiovascular disease, mostly in those with disease of the mitral valves. This group also showed a longer duration of heart failure. Long-standing pulmonary congestion, therefore, is a significant factor in the causation of pulmonary infarction.

The data indicate that jaundice is not directly correlated with the degree of anoxemia induced by pulmonary infarction. If it were true that the occurrence of frank jaundice depended wholly on the existence of an advanced degree of anoxemia, a much higher incidence of jaundice would occur in the cases of multiple and massive infarctions and of lobar pneumonia. Yet the existence of a pulmonary infarct appears to be an almost indispensable factor in the causation of clinical jaundice, occurring in 94 per cent of the cases. However, a combination of circumstances and factors is necessary.

In addition to long-standing pulmonary congestion, a higher incidence of anatomic lesions of the liver and of systemic or pulmonary infection is found in the patients with jaundice. A survey of the anatomic lesions of the liver and studies of the function of the liver make it apparent, however, that unless true cardiac cirrhosis or diffuse inflammatory vascular disease of the liver exists, the jaundice is not primarily of hepatic origin. Infection either systemic or pulmonary also plays an important contributory rôle, probably by influencing the rate of formation and resorption of bilirubin from its source, the pulmonary infarct, and the rate of its excretion by the liver.

Stroud, William D., Goldsmith, Melville A., Polk, D. Stewart, and Thorp, Francis Q.: Ten Years' Observation of Children With Rheumatic Heart Disease. J. A. M. A. 101: 502, 1933.

The present study of the condition of 458 children cared for at the Children's Heart Hospital in Philadelphia during a ten-year period from June, 1922 to January, 1932, with a more intensive study of some 141 children in this group selected because of the more complete data available in their case histories, may help to answer the query and at the same time, offer a contribution of additional information concerning rheumatic fever in children.

The average age of the primary manifestation of rheumatic fever in this group has been 7.3 years. Of the 307 children concerning whom information was available, 125 are dead or totally disabled and 182 are working or able to work or go to school. Of a total of 428 primary manifestations and reactivations concerning which positive information is available, 61 per cent occurred during and between the months of December and May with a peak of 15.2 per cent during March. It is suggested that during these months, prophylactic measures should be especially stressed in susceptible children between the ages of six and ten years, the years during which primary manifestations and reactivations are most

apt to occur. In this group, by far the greatest number of patients were of Italian, Hebrew, American, and Irish parentage, in the order named. There seems to be a familial incidence at least as high as that in tuberculosis.

Accurate information as to the incidence of common colds, sore throats, and other infections of the respiratory tract in other members of the family and their relationship to primary manifestations and reactivations of rheumatic fever cannot be obtained by questioning the child or his parents unless this problem and its possible importance has been carefully explained beforehand and frequently reiterated to the patient and each member of the family. Measures to protect children with rheumatic heart disease from the common cold and other infections of the respiratory tract offer as far as the study has shown, the most practical form of prophylactic treatment that at the present time can be freely recommended. The use of intravenous preparations of hemolytic streptococci with the hope of lessening hypersensitivity is still in the experimental stage but offers much promise.

Although positive proof that the routine removal of tonsils prevents primary manifestations or minimizes reactivations of rheumatic fever is not clear, it is felt by the authors that such a procedure plus a careful study of the sinuses is still justified in the type of child included in this study.

Premature contractions were found with relative infrequency in this group and auricular fibrillation was usually a terminal or near terminal event. The valve or number of valves involved in rheumatic heart disease in childhood has little to do with prognosis as compared to the virulence of the infection, the resistance of the host, and the number of reactivations.

It is felt, in conclusion, that a continuance of the treatment of children with rheumatic heart disease in convalescent hospitals in those areas in which rheumatic fever is prevalent is still justified.

Kugel, M. A., and Stoloff, E. Gordon: Dilatation and Hypertrophy of the Heart in Infants and in Young Children. Am. J. Dis. Child. 45: 828, 1933.

A complete review of the literature of congenital idiopathic hypertrophy of the heart has been made and the 52 cases found have been analyzed. In addition, the complete clinical, roentgenological, and pathological study of 7 additional cases from the authors are described. A careful study revealed that of these 52 cases only 17 were apparently associated with pure hypertrophy of the heart muscle both on gross and miscroscopic examination. In the light of the authors' experience with the 7 additional cases of dilatation and hypertrophy of the hearts in infants and children, all the cases reported in the literature have been re-examined.

In the cases studied, careful histological examination of the heart muscle showed uniformly similar pathological changes in the group of cases generally called congenital idiopathic hypertrophy of the heart. These pathological changes are degeneration and atrophy of cardiac musculature, replacement, fibrosis, scarring of the myocardium, endocardial fibrosis, and vascular changes. A thorough analysis of the roentgenograms was made in 4 cases. Significant electrocardiographic changes have been reported in one case. It seems from this study that the group of cases of so-called congenital idiopathic hypertrophy is probably seldom, if ever, idiopathic as has been demonstrated with the newer knowledge of the pathology and of the other factors causing dilatation and hypertrophy of the heart.

When the hearts are examined by the standardized sections of Gross, Antopol and Sacks and also numerous sections along the coronary arteries, it is possible to find myocardial degeneration and fibrosis.

Blumgart, Herman L., Riseman, Joseph E. F., David, David, and Berlin, David D.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity. Arch. Int. Med. 52: 165, 1933.

This communication is a report on the therapeutic results of total ablation of the normal thyroid gland in a series of ten patients with congestive heart failure or angina pectoris. The clinical observations which provided the rationale for this procedure are as follows: Measurement of the velocity of blood flow through the lungs in more than 600 subjects demonstrated that normally the velocity of flow was directly determined by the metabolic demands of the body. The metabolic demands of the body were gauged by the basal metabolic rate. When the metabolic rate was accelerated, as in thyrotoxicosis, the speed of blood flow was proportionately increased; on the other hand, when the metabolic rate was depressed, as in myxedema, the blood velocity was correspondingly lowered. Patients with compensated heart disease were found to have a blood velocity within normal limits, in accord with the normal level of the basal metabolic rate. But in subjects with congestive heart failure, in spite of a normal metabolic rate, the blood velocity was considerably slowed. This lack of correspondence offered an explanation for the presence of the symptoms and signs of decompensation which were in proportion to the degree of slowing of the blood velocity. The corollary of these observations was obvious: since therapeutic attack directed toward the circulation in chronic heart failure is unavailing, the way to relieve the circulation is to decrease the load on it by lowering the basal metabolic rate, i.e., by thyroidectomy. Subtotal thyroidectomy produced only temporary improvement.

Attacks of angina pectoris, which were present in two patients before operation, have not recurred since complete thyroidectomy. In one of these patients, before operation the same measured amount of work under standard conditions regularly precipitated attacks. After operation, under the same conditions, as much as six times the same amount of work was performed without attacks of angina pectoris, the exercise being finally terminated because of physical exhaustion. Seven of the nine patients with congestive heart failure had practically no cardiac reserve after prolonged periods of adequate medical treatment with complete rest in bed, so that the ability to be up and about without symptoms or signs of congestive failure could be attributed confidently to the effects of operation.

During the period of observation of three to six months that have elapsed since operation, all of the patients have shown conspicuous improvement. They have been able to undertake from slight to considerable exertion without the development of palpitation, dyspnea or any signs of congestive failure. The preoperative craving for water has disappeared. The basal metabolic rate of each patient has shown a significant and persistent lowering which has paralleled the most striking improvement. The velocity of blood flow has become slower in seven patients, indicating that the heart is required to do less work under the new postoperative condition than it was able to accomplish when the metabolic rate was normal. These patients may therefore be regarded as being in possession of a definite "cardiac reserve." The vital capacity of the lungs showed a decided increase in some patients though not in all. The significance of these findings is discussed. By means of exercise tests standardized for each of the nine persons with congestive failure, an increased ability to perform light work after operation has been demonstrated. Frequently recurring hemoptysis and pain in the chest have disappeared following operation. One patient who suffered

from paroxysmal dyspnea showed improvement for three weeks following operation. On the twenty-second day, he suffered from an attack of acute pulmonary edema during which he died. Further experience is necessary to evaluate the possible benefit to be derived from thyroidectomy in this condition and operation should be undertaken in this type of cardiovascular disease with extreme caution.

Following operation patients have had slight dryness of the skin, increased sensitivity to cold, slow growth of hair, and a lower heart rate. Thyroid substance has not been given except for short periods to two patients; in the others, it has not been indicated thus far. The medical management of the operative course is described. In one patient with congestive failure who had suffered from continuous attacks of bronchial asthma since childhood, no severe attacks have occurred since operation. The possible beneficial effects of the procedure in other conditions are discussed.

Because of the inevitable uncertainty as to the ultimate duration of the beneficial results, we feel that this operation should be undertaken at the present time only on patients with congestive failure or angina pectoris, in whom the operative risk is fair and in whom all other medical procedures have been employed without the desired therapeutic results. Patients with active coronary disease, active infection, vascular accidents, repeated pulmonary infarctions or rapidly progressive syphilitic cardiovascular disease are probably unfavorable subjects.

Rytand, David A.: The Effect of Digitalis on the Venous Pressure of Normal Individuals. J. Clin. Investigation **12**: 847, 1933.

Digitalis causes in normal human beings and dogs a decreased cardiac output and a decreased venous pressure. The greatest effect occurs at about twenty-four to thirty-two hours after administration of the drug with a return to normal level in from seventy-two to ninety-six hours.

The observed changes support the hypothesis that digitalis owes its action to a peripheral effect, probably on the hepatic vein radicles in reducing the return flow of blood to the heart. The hypothesis that the digitalis action follows changes in the cardiac tone is not supported by all available data. Digitalis bradycardia is not due to the fall of venous pressure; on the contrary, the slowing of the heart by causing the normal increase in venous pressure, partially conceals the effect of digitalis in reducing the return flow of blood to the heart.

Lehman, A. J., and Hanzlik P. J.: Comparative Potency of Some Digitalis Specialties According to the Pigeon Method. J. Pharmacol. and Exper. Therap. **48**: 151, 1933.

The potency as indicated by the minimum emetic and fatal doses for pigeons of several digitalis specialties has been compared with official tinctures from an American leaf and from an international powder used as standards. All the specialties caused emesis, their potency varied considerably, their keeping qualities during periods of months were good in the majority of cases but three of the specialties weakened considerably, their fatal doses varied considerably, and, in general, the killing power of the weaker specialties was out of proportion to their emetic efficiency, confirming previous results with ordinary digitalis. These specialties are no freer from side actions and have no special advantages over the ordinary official powder or tincture for general therapeutic uses except possibly the injection feature which may be useful in occasional special cases where

oral administration is impossible or undesirable and when emergency medication is indicated. The fact that some of the specialties do not keep nearly as well as the ordinary tincture is decidedly against them.

Tolerance to the emetic action of digitalis is demonstrable in pigeons which have been reinjected six times consecutively for ten weeks in agreement with reported loss of emetic action in reinjected dogs and cats. The tolerance does not impair the usefulness of pigeons for biological essay.

Schmitz, Henry Lenzen: Studies on the Action of Diuretics. II. The Effect of Salyrgan Upon the Water Content of the Plasma as Measured by the Refractive Index. J. Clin. Investigation **12**: 741, 1933.

The effect of salyrgan upon the water content of the plasma has been studied by means of the refractometer in dogs. There is no evidence in the experiments that salyrgan diuresis is preceded by a mobilization of fluid from the tissue spaces. The results point strongly to a primary direct action of salyrgan on the kidney with a secondary inflow of fluid from the tissue spaces to prevent excessive dehydration of the plasma.

Weiss, Soma, and Ellis, Laurence B.: Influence of Sodium Nitrite on the Cardiovascular System and on Renal Activity. Arch. Int. Med. **52**: 105, 1933.

The study concerns the effect of large therapeutic doses (from 1 to 5 grains) of sodium nitrite by mouth on ten normal persons, twenty-nine patients with primary arterial hypertension, five patients with glomerulonephritis, and nine patients on whom unilateral nephrectomy had previously been performed. Qualitatively the effect was the same in each group, but there were certain quantitative differences between the normal subjects and those with hypertension and renal disease.

The nitrite inconstantly produced symptoms, an increase in cardiac rate and a depression of blood pressure and renal function. No simple correlation was found between these factors except when they were markedly altered.

A decrease of systolic blood pressure was the most frequently observed effect of sodium nitrite. This was caused probably by dilatation of certain parts of the arterial system. The greater the initial degree of arterial tonus, the greater was the drop in systolic pressure. With arterial hypertension, this was particularly evident.

In five normal persons sodium nitrite produced no change in the minute volume output of the heart. In five patients with arterial hypertension this output was doubtfully reduced in three, and reduced 15 and 32 per cent respectively in two. In nine of these ten subjects there was a reduction of the cardiac stroke volume output, which reached 15 per cent or more in six.

Sodium nitrite did not affect the basal metabolic rate of nine of ten subjects; it possibly increased the rate in one.

The effect of the nitrite on renal function was investigated thirty-five times by simultaneous determinations of the urinary output and urea and creatinine clearance tests. In no case was the renal capacity improved. In fourteen instances there was no change in renal function; thirteen times it was definitely decreased, and on eight occasions it was questionably lowered.

Physiologic changes which occur in the human cardiovascular system as a result of the action of sodium nitrite are discussed and correlated.

The use of sodium nitrite in the routine treatment of arterial hypertension with the hope of maintaining the blood pressure at a relatively low level is illogical and may be dangerous.

Evans, William, and Hoyle, Clifford: The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris. Quart. J. Med. 2: 311, 1933.

A series of 90 patients with angina pectoris of effort was observed over a period of two and a half years, with special reference to the comparative value of certain drugs and medicinal remedies with any claim to be applied in continuous treatment. Syphilitic angina pectoris was excluded and coronary thrombosis was only considered as a complication.

Each patient attended fortnightly and the various drugs were administered over periods of two to four weeks at a time, or longer. In this way their effects upon the frequency and severity of attacks could be compared. As a control in each case a placebo was regularly substituted for an active drug. The following drugs were tested: sodium nitrite, mannitol hexanitrate, erythrol tetranitrate, potassium iodide, luminal, chloral, morphine, papaverine, phenacetin, diuretin, euphyllin, belladonna, digitalis, lacarnol, and harmol.

The comparative results are outlined in tables and graphs. With one exception, they show that a measure of improvement appears to result from every remedy tried and at least as great an improvement during treatment with placebo. This universal efficacy can only be explained by natural variations in the severity of the symptoms which give a spurious value to each remedy. If any drug had proved to be superior, there might have been grounds for recommending it in the continuous treatment of the disease, but no such precedence could be made out. Though scarcely convincing, there was some reason to think that chloral, morphine, papaverine and phenacetin had a trifling influence in controlling the group incidence and severity of attacks.

The authors were unable to find convincing evidence that any drug tested is worthy even of trial in the routine treatment of the disease. Though not widely applicable, a drug might of course be effective in individual cases, and examples were sought for, but, with a few exceptions, were not found. The nature of the underlying cause of angina pectoris alone would seem to make the quest for a satisfactory form of treatment on these lines unlikely of attainment.

If none of these remedies are capable of lessening the frequency or severity of anginal attacks, there is all the greater need for a study of the application of those general measures known to control them and to promote the wider use of vasodilators, such as trinitrin, which are so often successful in the palliative treatment or even in the prevention of particular attacks.

Starr, Isaac, Elsom, K. A., and Reisinger, J. A.: Acetyl-β-Methylcholin. Am. J. Med. Sc. **186:** 313, 1933.

In experiments on 47 normal persons, acetyl-β-methylcholin chloride has proved to be a drug which when injected subcutaneously in suitable dosage exerts a prompt and vigorous action. A fall in blood pressure, a rise of pulse rate, flushing, sweating, and salivation are the outstanding effects. Given by mouth this drug has a milder effect than that following subcutaneous injections. Given by the former method, even in very large doses, it does not cause discomfort, although blood pressure and pulse rate changes have been noted. The dosage required to produce effects by mouth is so much larger than when given subcutaneously that the destruction of large amounts of the drug in the gastrointestinal system seems probable.

In animal experiments an intravenous injection of acetyl-β-methylcholin chloride has effects on the cardiovascular system essentially similar to those which follow acetyl cholin, but judging by the effects which follow subcutaneous injections into normal men, acetyl-β-methylcholin chloride is over ten times as

powerful. It can also be given by mouth, whereas acetyl cholin is ineffective when thus administered. It also lacks certain of the undesirable side effects of acetyl cholin. It is believed, therefore, that acetyl-β-methylcholin chloride should supplant acetyl cholin in all conditions in which that drug is used for therapeutic purposes.

Abbott, W. Osler: Acetyl-β-Methylcholin. II. The Action on the Gastrointestinal Tract in Normal Persons, in Abdominal Distention and in Certain Other Conditions. Am. J. Med. Sc. **186:** 323, 1933.

Acetyl-β-methylcholin by whatever route given affects the gastrointestinal tract as well as the other viscera supplied by the parasympathetic system. This effect is most satisfactorily achieved by oral administration, secretory and cardiovascular activity dominating the picture after subcutaneous injection.

The usual gastrointestinal effects are an increase in tone and movement. This is not the case in the fasting stomach or in the small intestine during the period of falling pressure after subcutaneous injection. Beneficial clinical effects have been manifested by slight stimulation of gastric secretion in some cases of hypochlorhydria, by a comfortable laxative effect in most persons taking large doses by mouth, but chiefly by the relief of abdominal distention in certain instances in which the usual procedures have failed.

Starr, Isaac: Acetyl-β-Methylcholin. III. Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease, With a Discussion of Its Action in Other Conditions. Am. J. Med. Sc. **186:** 330, 1933.

Acetyl-β-methylcholin has been employed in the treatment of certain types of cardiovascular disease. This drug causes effects similar to those following stimulation of the vagus and other parasympathetic nerves. It also causes peripheral vasodilatation. After subcutaneous injection, it has a prompt and vigorous action. Given by mouth the effects are much milder. The untoward effects of the drug are described; they can be immediately abolished by atropine.

Injected subcutaneously the drug has caused the immediate termination of twenty-four attacks of paroxysmal tachycardia in 9 patients. In most of the attacks carotid pressure and other means had been tried unsuccessfully before the drug was given. In a few instances a combination of the drug's action and carotid pressure terminated attacks which could not be stopped by carotid pressure alone. Failure was very infrequent except when the dosage was inadequate.

The vascular spasm of Raynaud's disease when excited by mild degrees of cold was relieved or prevented by the action of the drug administered by mouth. The spasm following exposure to severe cold was but little affected. The discomfort of three such patients was in part ameliorated by taking the drug by mouth during cold weather.

The drug repeatedly caused a rise of the skin temperature of the feet in a patient with thromboangiitis obliterans. It caused a temporary reduction of blood pressure in most cases of hypertension. In one patient Cheyne-Stokes respiration was abolished by the drug. The possible utility of acetyl-β-methylcholin in certain other disease conditions is discussed.

Book Review

THÉRAPEUTIQUE MÉDICALE. VI. COEUR ET SANG. By MM. A. Lemaire, E. Donzelot, Ch. Aubertin, A. Clerk, G. Marchal, R. Boigey, M. Mouquin, P. Émile-Weil, A. Tzanck. Pp. 312. Masson & Cie. Paris, 1933.

This volume is the sixth in a series of seven which comprise a system of therapeutics prepared under the editorship of Professor M. Loeper. It is evident from the list of contributors that this volume represents the best modern French opinions concerning the therapy of diseases of the heart and of the blood. The volume is divided into four parts, the first of which comprises the drug therapy of the various types of cardiac disease and of syncope and is chiefly from the pen of Professor Loeper. The second part is a presentation of the dietetic régime for the treatment of the cardiopathies. The third deals with the treatment of arrhythmia and the fourth with diseases of the blood.

The material is well arranged and the discussion of the employment of the various therapeutic agents is preceded by a brief but clear résumé of the pathological physiology, of the symptoms and manifestations of the diseases, as well as by discussion of the chief points in the pharmacology of the agents recommended. The agents are divided into those of major importance, such as digitalis, ouabain, etc., those of minor importance, and those which, while not acting upon the heart or blood vessels in any specific manner, can be regarded as adjuvants.

The chapter on the treatment of the various forms of cardiac failure emphasizes almost exclusively the French viewpoint which gives special preference to the use of Nativelle's digitaline (the crystalline digitoxin of the Germans) and Arnaud's ouabain (crystalline strophanthin G.). Detailed directions are given for their dosage and administration which do not differ essentially from those employed by others. Much emphasis is laid upon the value of glucose and of calcium as supportive measures in the treatment of heart disease and measures which materially enhance the activity of the digitalis bodies. It is rather striking to note the seeming impunity with which the administration of insulin is advocated in the treatment of cardiac failure. This is based primarily upon the conception of the value of glucose as a nutrient to the heart, and the corollary, that its utilization is enhanced by the simultaneous administration of insulin. Throughout the book many remedies are advocated as adjuvants which have largely been rejected in America.

The section on diseases of the blood is rather too brief and is somewhat incomplete. The authors have entirely omitted the discussion of polycythemia vera, even though it was originally described by one of their own countrymen, Vaquez. The treatment of pernicious anemia is taken almost bodily from the work done in America.

While the book is well printed and well arranged, it is distinctly marred by the absence of any adequate bibliography and by the absence of an alphabetical index. The relatively small number of references which are given show a considerable number of seemingly careless inaccuracies. Despite these shortcomings, the volume is an excellent one and should prove of real value to those interested in the methods of treatment found best by the leading therapists of France.

C. E.